THE EFFECT OF SEVERAL PHYSIOTHERAPEUTIC INTERVENTIONS ON TRACHEOBRONCHIAL CLEARANCE

Evaluation by means of measurement
of tracheobronchial clearance
using a radio-aerosol technique

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The research in this thesis was performed in the Department of Nuclear Medicine (head: Prof.Dr. F.H.M. Corstens) and the Department of Pulmonary Diseases (head: Prof.Dr. C.L.A. van Herwaarden), University Hospital Nijmegen, The Netherlands.

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ANOVA	analysis of variance
AUC	area under the curve
AUC-2	area under the curve 0-2 hours
AUC-4	area under the curve 0-4 hours
AUC-6	area under the curve 0-6 hours
AUC150	area under the curve 0-150 minutes
AUC 2.5	area under the curve 0-150 minutes
CB	chronic bronchitis
COV	coefficient of variation
CONV	conventional physiotherapy
DC	dextrocardia
FEF_{25-75}	mean forced expiratory flow during the middle half of the forced vital capacity
FET	forced expiration technique
FEV_1	forced expiratory volume in one second
FOT	forced oscillations technique
FVC	forced vital capacity
GSD	geometric standard deviation
^{81m}Kr	krypton-81m
KS	Kartageners' syndrome
MEF_{50}	maximal expiratory flow at 50% FVC
MRC	Medical Research Council
OHFO	oral high frequency oscillation
PD	postural drainage
PEP	positive expiratory pressure
PI	penetration index
PIT	post inhalation time
SD	standard deviation
sGaw	specific airway conductance
^{99m}Tc	technetium-99m
TBC	tracheobronchial clearance
TBR	tracheobronchial retention
TBRet	tracheobronchial retention
VC	vital capacity

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Een wetenschappelijke proeve op het gebied
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Aan de nagedachtenis van mijn vader

Contents

General Introduction

Tracheobronchial clearance is defined as the sum of the effect of cough and mucociliary transport. In normal circumstances mucociliary transport alone is sufficient with regard to clearance of the airways. When, for instance during respiratory tract infections, mucociliary transport is impaired cough may occur. Cough appears to be the most frequent complaint for which the general physician is consulted.[1,2] Remedies for the treatment of cough belong to the most popular pharmaceutical preparations. When troublesome expectoration prevails treatment consists not only of drugs but quite often also of physical therapy aiming at mobilization of secretion. Many patients highly value these respective treatments. Objective evidence of clinical efficacy appears to be rather poor though. Parameters used for evaluation of the effectiveness have been lung function, blood gas analysis, frequency of exacerbations in chronic lung disease and especially scoring by the patients themselves. Because these treatment modalities are supposed to enhance the mobilization of secretion the most appropriate parameter for evaluation thereof seems to be the measurement of tracheobronchial clearance itself. In view of the need for more objective evidence whether or not several mucolytics and physiotherapy regimens were effective it seemed therefore obvious to us to use for this purpose the measurement of tracheobronchial clearance. In 1967 Booker et al[3] described a radio-aerosol technique for the in vivo measurement of tracheobronchial clearance in human beings. Thomson and Short[4] reported the results of the measurement of tracheobronchial clearance using this technique in healthy subjects, in patients with chronic obstructive lung disease and with asbestosis. As of 1984 the measurement of tracheobronchial clearance using a technetium-99m (^{99m}Tc) labelled polystyrene aerosol was applied in the department of Nuclear Medicine in the University Hospital Nijmegen.

To begin with a study was performed in order to assess variability of tracheobronchial clearance in healthy subjects. The results of this study are described in chapter II.

Conventional physiotherapy consisting of postural drainage, chest percussion and instructed coughing has been the most frequently applied physiotherapy regimen during the last decades. A relatively new technique is the forced expiration technique. This includes breathing exercises, huffing and usually postural drainage. The forced expiration technique has been advocated as being effective and more convenient than conventional physiotherapy especially for patients who require daily treatment.[5] In chapter III the results of a study in which the conventional physiotherapy is compared with the forced expiration technique are reported.

More recently positive expiratory pressure mask breathing was reported as being a convenient and effective method for the mobilization of bronchial secretion.[6] Especially in centres for the treatment of cystic fibrosis this technique has become very popular. The effect of positive expiratory pressure on tracheobronchial clearance was investigated comparing this with the forced expiration technique. The results of this study are reported in chapter IV.

Oral high frequency oscillation can be considered as an experimental technique originating from high frequency ventilation. As it seemed to be an elegant technique to enhance tracheobronchial clearance[7] its efficacy in this respect was investigated and has been reported in chapter V.

Quite often chest physical therapy is combined with the use of inhaled mucolytics. In order to be able to determine whether the effect of this type of treatment is due to its mucolytic action, its hypertonicity causing an osmotic reaction, or a simple wetting effect the study described in chapter VI was performed. An inhaled mucolytic, hypertonic or isotonic solution was combined with physiotherapy. Their effects on tracheobronchial clearance were compared with each other.

Tracheobronchial clearance in a group of patients with dextrocardia is described in chapter VII.

Finally in chapter VIII a study of the effect of sauna on tracheobronchial clearance in patients with chronic bronchitis is reported.

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Chapter I

I.1 Tracheobronchial clearance, a brief survey of the literature

I.1.1 Definitions

Mucociliary transport is defined as the movement of mucus due to ciliary beating.

Cough is another mechanism aimed at clearing the airways. It occurs usually when for some reason mucociliary transport is not sufficient.

Tracheobronchial clearance is defined as the sum of the clearance by mucociliary transport and cough.

Alveolar clearance is the mechanism by which the most distal airways and alveoli are kept clean.

Whole lung clearance is commonly defined as the sum of tracheobrochial clearance and alveolar clearance.

Three mechanisms play a major role in the deposition of particles in the airways. These are inertial impaction[1,2], gravitational sedimentation[2] and Brownian diffusion.[2] Minor mechanisms are electrical forces, thermophoresis and simple contact with the airway wall. The site of deposition of an inhaled particle depends on its physical and aerodynamic properties. This site determines to a large extend the mechanism through which the particle is removed from the airways. The airways extending from the respiratory bronchioli down to the alveoli are considered as the non-ciliated regions. These are kept clean mainly by means of phagocytosis. This clearance mechanism is referred to as alveolar clearance. In the remaining lower airways i.e. from the trachea down to the terminal bronchioli the lumen is lined with ciliated epithelium. Under normal conditions here mucociliary transport is responsible for the removal of particles, excess secretion, cellular debris etc. Cough occurs under several pathological conditions among which impaired mucociliary transport. On theoretical grounds it is assumed that cough can only be effective in mobilizing secretion from the level of the trachea down to the 8th generation of Weibel's model of the lung.[3]

I.1.2 Normal structure and function of airway epithelium

The epithelium lining the airways from trachea to terminal bronchioli consists mainly of two cell types. These are the ciliated cells and the goblet cells. There are some additional rarer cells, such as neuro-endocrine cells, which are capable of secreting certain mediators into the blood, and so-called brush cells, whose function is not yet understood. In the proximal airways there are approximately 5 ciliated cells to each goblet cell. The relative numbers of goblet cells and ciliated cells decrease towards the peripheral airways. It has been estimated that each ciliated cell contains about 200 cilia. Tracheal cilia are 5-6 micrometer long and 0.2-0.3 micrometer in diameter. In the peripheral airways cilia are shorter. All normal cilia have nine pairs of peripherally located microtubules and two central microtubules.[4] Bronchial mucus is mainly produced by goblet cells and submucosal glands. It consists for 95% of water. Apart from glycoproteins it contains also cells, debris and surfactant. It forms a fluid film lining the airway epithelium. In this fluid film commonly two more or less separate layers are distinguished, which are referred to as the sol and the gel phase. The sol phase is the periciliary layer. The gel phase is the outer more viscous layer, which the cilia reach only with their tips during the effective stroke of ciliary beating. The main macromolecular component of airway mucus are glycoproteins. Intramolecular and intermolecular disulphide bonds of glycoproteins are for a large part responsible for the gel structure of the outer layer.

Relatively little is known about the regulation of secretion by the goblet cells and the ciliated cells. Irritants seem to play a major role here rather than neurohumoral or reflex mechanisms.[5] The regulation of secretion by the submucosal glands is under parasympathetic and adrenergic control. Several phenomena induce an increase of secretion via vagal reflex pathways. For instance inflammation, hypoxia and gastric distension have been described as such.[6]

I.1.3 Mucociliary transport

Mucociliary transport can be considered as a non-specific host defence mechanism of the lung. Adequate ciliary motion and the presence of mucus are the prerequisites for mucociliary transport. Movement of the cilium is achieved by sliding of adjacent microtubular doublets. Ciliary beating consists roughly of two phases. These are the effective stroke and the recovery stroke. During the effective stroke the extended cilium reaches with fine claws on its tip into the gel phase thereby propelling it forward i.e. in the direction of the epiglottis. During the recovery stroke the cilium bends in the periciliary layer (sol phase) thereby sliding beneath the gel phase. Cilia beat at frequencies around 10-20 Hz. Within groups of cilia beating occurs in a coordinated fashion. This coordination not only implies that cilia beat in the same direction but also that cilia beat one after another causing a wave-like motion. Under normal conditions ciliary beating results in a mucus velocity of 0.5 mm/min in the peripheral airways gradually increasing centrally up to 15 mm/min in the trachea. The gel-like structure of airway mucus enables the transfer of energy from ciliary motion to the gel phase and is therefore essential for effective mucociliary transport.[7,8] The quantity of mucus transported by the mucociliary escalator is estimated as ranging from 10 to 100 ml/24 hrs in healthy individuals.[9]

I.1.4 Cough

Cough is induced voluntarily or by reflex mechanisms via cough receptors. Cough begins with an inspiration. Then the glottis is closed. Expiratory muscles subsequently build up pressures up to 13 kPa or more in the airways. This compressive phase is followed by the expiratory phase when the glottis is opened abruptly. Cough can only be effective in mobilizing secretion from the level of the trachea down to the 8th generation of Weibel's model of the lung.[3] The effectiveness of cough is closely related to the peakflow achieved during the expiratory phase as well as the duration thereof. Furthermore the viscoelastic properties of airway mucus are of importance.

I.2 Tracheobronchial clearance and disease

I.2.1 Chronic bronchitis

According to the MRC chronic bronchitis is defined as chronic or recurrent increase in the volume of mucoid secretion sufficient to cause expectoration on most days, for at least three months of the year, over two successive years.[10] Smoking is considered to be the most frequent cause of chronic bronchitis. Hilding suggested that mucociliary dysfunction is the first abnormality in chronic bronchitis.[11] Mucociliary transport has been demonstrated to be impaired in patients with chronic bronchitis.[12] Airways obstruction is a common feature in longstanding chronic bronchitis. There appears to be no relationship between impairment of mucociliary clearance and the degree of airways obstruction though.[9] In chronic bronchitis the following structural changes in the mucosa have been described: hypertrophy and hyperplasia of submucosal glands, change in distribution and increase in number of goblet cells, loss and abnormal regeneration of cilia, edema and infiltration of the mucosa with inflammatory cells.[13] The presence of excess mucus predisposes to colonization of the lower airways with pathogens and eventually to overt respiratory tract infections leading to further impairment of mucociliary clearance.[14]

I.2.2 Asthma

In mild stable asthma mucociliary transport has been shown to be impaired.[15] Even in asymptomatic asthmatics tracheal mucus velocity appeared to be decreased.[16] Certain qualitative changes in mucus in asthmatics could have a negative effect on its rheologic properties.[17] Also it has been shown that e.g. antigen inhalation[18], certain leukotrienes[19] and histamine[20] cause an increase in mucus production. Both these changes and epithelial damage inevitably lead to mucociliary dysfunction. Postmortem studies in patients who died in a status asthmaticus have revealed extensive desquamation of the bronchial mucosa with widespread mucous plugging of small airways.[21,22] So in severe asthma the mucociliary apparatus seems to be seriously damaged.

I.2.3 Cystic fibrosis

Structural abnormalities in the lungs of patients with cystic fibrosis are: hypertrophy of submucosal glands, goblet cell metaplasia, and mucous plugging of peripheral airways.[23] Once there exists a persistent infection of the lower airways destruction of epithelium and squamous metaplasia occurs.

Eventually bronciectasis and airways obstruction develop. Tracheobronchial clearance has been shown to be impaired. In one study a relation between the degree of impairment of tracheal mucus transport and the Schwachman score, an index for clinical condition, has been reported[24], while others have been unable to confirm this.[25] Although it is a widely accepted view that the viscosity of bronchial secretion is increased in cystic fibrosis no study dealing with the rheologic properties of mucus has confirmed this.[26,27,28] Since Spock et al[29] reported the existence of a cilio-inhibitory serum factor in cystic fibrosis this finding still awaits final proof.

I.2.4 Primary Ciliary Dyskinesia

In 1933 Kartagener described four patients with the combination of situs inversus, sinusitis and bronchiectases.[30] This is referred to as Kartagener's syndrome. Earlier the bronchiectases in these patients were thought to be congenital. Today it is a widely accepted view that they are caused by recurrent purulent respiratory tract infections.[31] Kartagener's syndrome appeared to be associated to a high degree with infertility, although there have been reports of Kartagener patients with descendants.[32-35] Reports of sperm tail immotility focused attention on ciliary abnormalities as a possible cause of recurrent pulmonary infections.[36] Since 1976 several specific abnormalities in the ciliary ultrastructure associated with ciliary immotility or dyskinesia have been reported.[37-43] However Kartagener patients with normal cilia have also been described.[44,45] In conclusion there appears to exist a whole spectrum of congenital ciliary abnormalities of both structure and function in patients with and patients without situs inversus. Today this syndrome is reffered to as primary ciliary dyskinesia.[46] Despite the absence of an important host defence mechanism patients with this syndrome, patients with Kartagener's syndrome included, appear to have a relatively good life expectancy.

I.2.5 Respiratory infections

In naturally acquired common cold the mucociliary transport rate appears to be impaired up to 32 days after the first symptoms.[47] In influenza A infections mucociliary clearance was reduced for 3 months.[48] Impairment of mucociliary transport is probably caused by loss of and/or damage to ciliated cells. Furthermore an increase in bronchial secretion with abnormal rheologic properties may add to mucociliary transport failure. In bacterial infections of the lower airways there is also generalized mucociliary dysfunction, for which several mechanisms are responsible. Not only bacterial products but also proteases from leucocytes cause epithelial damage.[49] Several bacteria (Pseudomonas aeruginosa, Haemophilus influenzae, Bordetella pertussis and Streptococcus pneumoniae) also produce factors which have been shown to reduce ciliary beat frequency in vitro.[50-53]

I.3 Measurement of tracheobronchial clearance

The mucus flow in the bronchial tree can only be measured using marker(s) of the mucus layer. Markers which have been used amongst others are: teflon discs, bismuth coated radiopaque discs, tantalum powder, radiolabelled albumin microspheres, and several types of radio-aerosol (teflon, albumin aggregates, iron oxide, erythrocytes, resin and polystyrene).

There are several techniques to monitor the displacement of the marker(s) caused by tracheobronchial clearance. Direct visualization can be achieved by means of a bronchoscope. Less invasive external measurement can be performed using roentgenographic equipment in case of radiopaque marker(s), scintillation detector(s) and gamma camera(s) after instillation or inhalation of radioactive marker(s).

The main techniques to assess mucus transport, of which some are still in use nowadays are the following. For the cinebronchofiberscopic technique[54], described in 1973, ten to twenty small teflon discs are blown into the trachea through a bronchoscope. Tracheal mucus velocity is calculated by measuring the time needed for the discs to move over a certain length. An alternative to this method implies the coating of the discs with a radiopaque substance (bismuth trioxide) and monitoring the displacement roentgenographically.[55] This technique was reported in 1978. In case of the radionuclide bronchoscopic technique[56] (1979) about 40 μl of a suspension containing albumin particles (5-7 μm in diameter, labelled to technetium-99m) is deposited near the carina by a catheter inserted through a bronchoscope. Movement of the particles is recorded by means of a gamma camera for half an hour. The techniques mentioned above all have the disadvantage of being rather invasive, thus disturbing normal physiological conditions. Yeates et al described in 1975 the radio-aerosol boli technique.[57] By inhalation at high flow and at near total lung capacity a bolus of aqueous aerosol of albumin microspheres with a median diameter of 0,5 μm and labelled with ^{99m}Tc is deposited in the central airways. A gamma camera is used for recording. This technique allows measurement in the central airways only.

In contrast to this method the radio-aerosol technique in general implies the inhalation of a radio-aerosol resulting in deposition along the whole bronchial tree. Inevitably some particles penetrate into the so-called non-ciliated regions of the lungs consisting mainly of alveoli. This is usually referred to as alveolar deposition. After inhalation intrathoracic activity is monitored by means of several types of external detectors. Gamma cameras with a parallel hole collimator allow assessment of the initial radio-aerosol distribution and of regional clearance when serial images over time are made.[58] Relatively high amounts of radioactivity are required for this type of recording though. Integral counting of intrathoracic radioactivity with a sodium-iodide detector with a wide angle collimator has a relatively high efficiency compared to a gamma camera. Therefore less activity is needed to obtain adequate statistical information. Two axially opposed detectors placed in front of and behind the subject enable the correction for movement of radioactivity towards or away from a detector.[59] Using this type of detectors it is important to apply such collimation that activity present in the throat or stomach is not counted effectively. The recording of the count rate over the chest at several points of time after inhalation provides information about the tracheobronchial clearance. The most important advantage of the radio-aerosol technique is its non-invasive character. Thereby it is possible, as mentioned above, to perform the measurement under physiological conditions. Another advantage is the small amount of radioactivity needed thus resulting in a low radiation dose to the lungs. Finally it comprises the clearance in all ciliated airways. Disadvantages of the radio-aerosol technique are the artefacts due to different deposition patterns and to cough.

Advantages and disadvantages of the several techniques are listed in table 1.

Table 1

Technique	Advantages	Disadvantages
Cinefiberscopic Roentgenograpic Radionuclide Bronchoscopic	1. short observation period 2. repeat measurements within a short period of time 3. measurement of clearance in well defined airways	1. invasive 2. limited to large airways only
Radio-aerosol boli	1. non invasive	1. low sensitivity due to slow transport rates
Radio-aerosol	1. non invasive 2. low radiation dose 3. measurement of clearance from all cliated airways	1. clearance depends on deposition pattern 2. long observation periods (up to 24 h) 3. artefacts due to coughing

I.4 Outline of the study

According to the technique described by Thomson and Short[60] a similar radio-aerosol technique was developed in the department of Nuclear Medicine of the University Hospital Nijmegen. For repetitive measurement of clearance it is essential to be able to realize a similar deposition pattern. Therefore the aerosol should preferably be monodisperse. The aerosol which was used in our department contained ^{99m}Tc labelled polystyrene particles. This aerosol was produced by means of a spinning top generator (R.E. May Spinning Top Aerosol Generator, Research Engineer Ltd.). Mean particle diameter was 5 μm (GSD = 0,80). Particle size, shape and presence of aggregates were checked regularly by examining slides left on the bottom of the aerosol tank, using a light microscope at a magnification up to 650 times. Not only the aerosol itself but also the inhalation procedure should be standardized. The equipment to achieve this was designed and built by the Department of Instrumentation of the medical faculty. A spirometer was linked in series to the tank in which the aerosol was produced, from which it was inhaled (see figures 1 and 2).

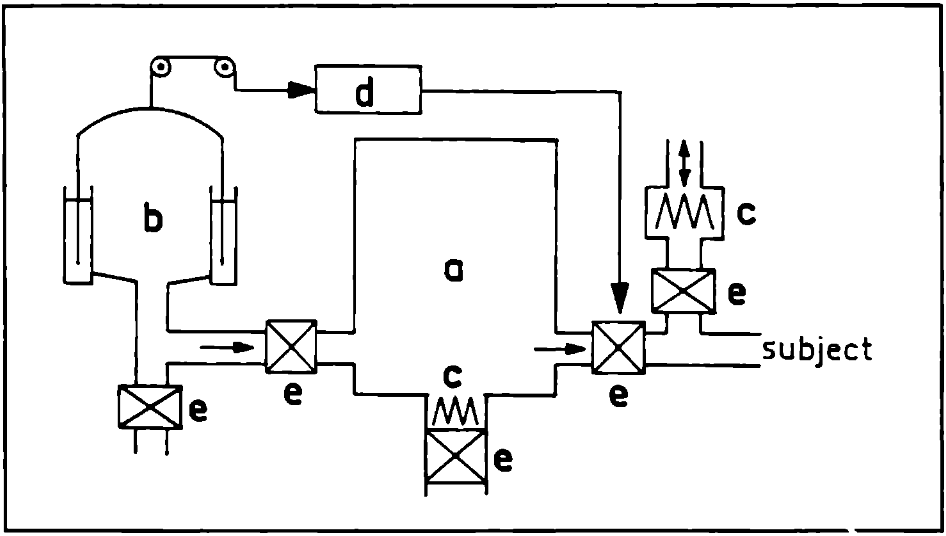


Figure 1. Schematic diagram showing the radio-aerosol inhalation unit.
(a) tank with aerosol generator, (b) spirometer, (c) filter, (d) recorder, (e) valve.

Thus it was possible to adjust the volume of the inhalations, aiming at 500 ml, and also record the flow of the inhalations. The inhalation procedure was as follows. To begin with the valve between subject and aerosol tank was shut and the subjects were breathing room air. At the end of an expiration, the valve between subject and aerosol tank was opened, while simultaneously the tube, through which the subject was breathing room air, was closed. After inhalation of the preset volume of radio-aerosol the valve between subject and aerosol tank was closed automatically. Then followed a 3-second breathhold. Subsequently the connection with the room air was opened and the subject was instructed to expire first, after which room air breathing

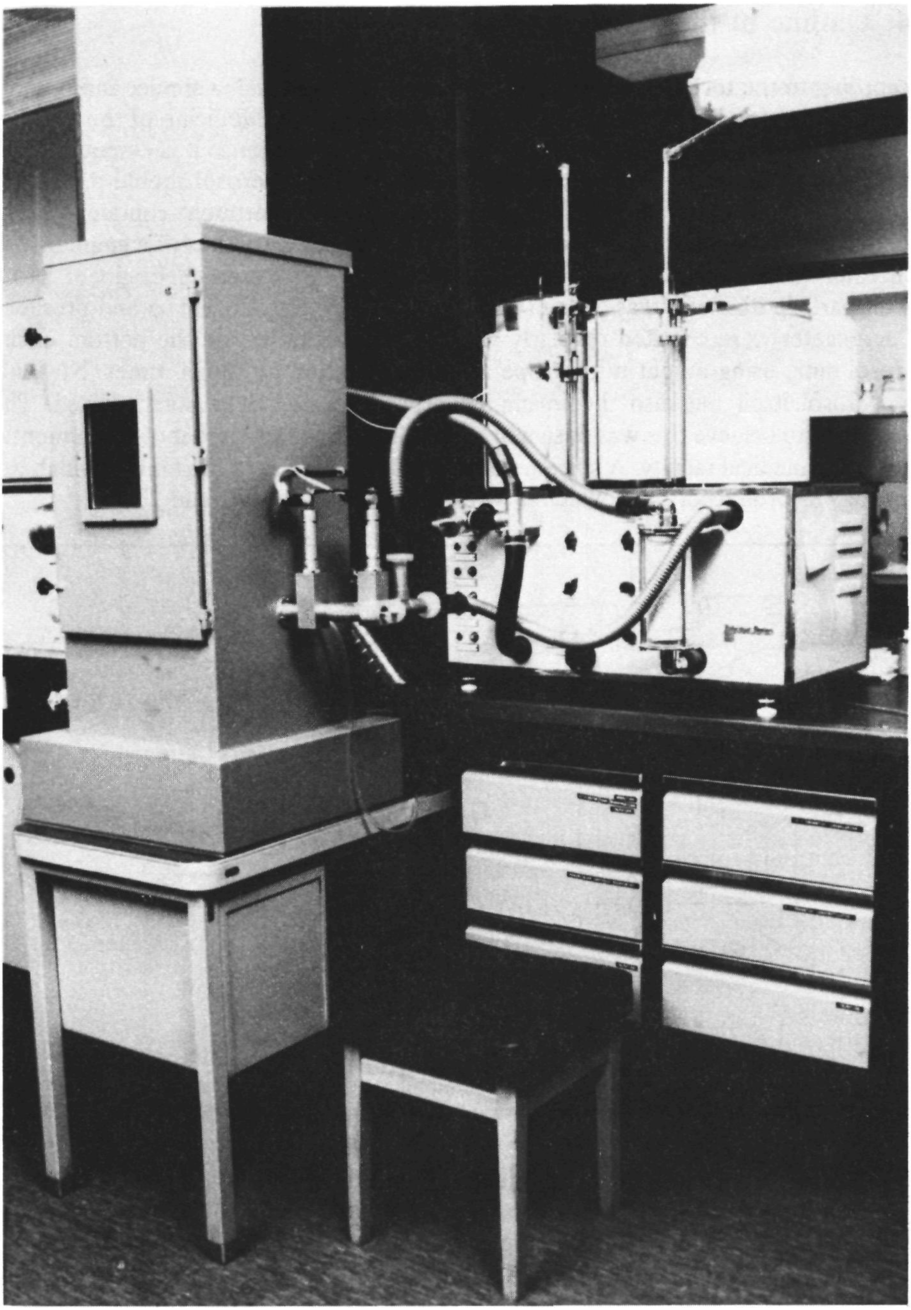


Figure 2. Radio-aerosol inhalation unit in the department of Nuclear Medicine of the University Hospital Nijmegen.

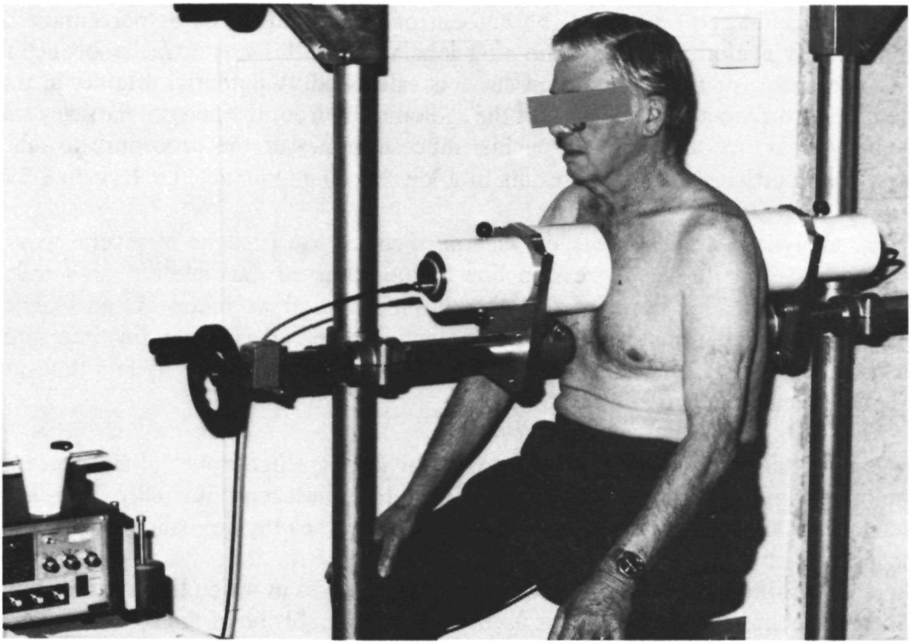
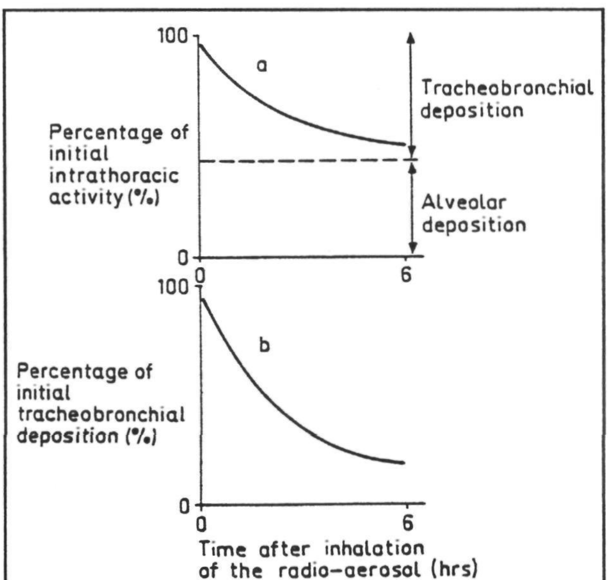


Figure 3. Subject positioned between the dual probe for the integral measurement of intrathoracic activity.

was resumed. This procedure was repeated up to 10 to 15 times, depending on the concentration of radioactivity in the aerosol. The subjects were instructed and trained to inhale at tidal breathing level. After inhalation of the radioaerosol intrathoracic activity was measured at regular intervals by means of a dual probe system (see figure 3). For the calculation of the tracheobronchial clearance the decrease in intrathoracic activity must be corrected for alveolar deposition (see figure 4). Because the physical half-life of the radionuclide ^{99m}Tc is only 6 hrs a correc-



Figuur 4. (a) Diagrammatic curve showing lung retention following inhalation of radio-aerosol; (b) Curve showing tracheobronchial retention i.e. lung retention after correction for alveolar deposition.

tion for decay has to be made. The amount of activity expressed as percentage of initial activity is plotted against time after inhalation. In this way a tracheobronchial clearance curve or rather retention curve is calculated. A potential artefact in this type of measurement is the release of the radionuclide from the aerosol particles followed by clearance across the bronchial mucosa. However the procedure to label polystyrene particles with ^{99m}Tc results in a low leaching tendency, i.e. less than 5% in 24 h.[61]

The analysis of tracheobronchial clearance curves can be done in several ways.[7] One method is to fit the regression line to the observed data plotted on semilogarithmic paper. The slope of this line has been used as index of mucociliary clearance. Other parameters used are the amount cleared at a certain time after inhalation, the time needed for clearance of 50% of the initial activity and the area under the clearance curve.

It was necessary to see whether the measurememt of tracheobronchial clearance as developed in our department showed sufficient intrasubject reproducibility. Therefore tracheobronchial clearance was measured twice in ten healthy non-smoking subjects. The results of our measurements appeared to be better than those reported by others using different techniques (see chapter II). Studies in which the measurement of the tracheobronchial clearance is used, should preferably be of the cross-over type because of the rather large intersubject variability. On the basis of our study and that of Del Donno et al[62] it is possible to determine the required number of subjects or patients needed to demonstrate a certain effect in a cross-over study (see discussion chapter II). Beforehand the minimum change in tracheobronchial clearance which is considered as being of clinical relevance must be determined.

After the evaluation of the variability of tracheobronchial clearance several studies were performed to assess the efficacy of several types of physiotherapeutic interventions. For these studies the randomized cross-over design was chosen. In the first study (chapter III) the effect of conventional physiotherapy on tracheobronchial clearance was compared with that of the forced expiration technique combined with postural drainage. The aim of the study was to compare efficacy of both treatment regimens as applied in daily practice. The patients participating in this study all required regular chest physical therapy. Also the design of the study was such that common every day practice was mimicked as closely as possible. Apart from the effect on tracheobronchial clearance regional lung clearance was evaluated as well. For this purpose gamma camera images were recorded before and after treatment. Since the results of this study clearly showed the efficacy of the forced expiration technique combined with postural drainage, this physiotherapeutic regimen was chosen in subsequent studies as standard chest physical therapy. In chapter IV the effect of positive expiratory pressure mask breathing, a relatively new method of physiotherapy, on tracheobronchial clearance and regional lung clearance was studied and compared with the forced expiration technique combined with postural drainage. In contrast with the study mentioned above (chapter III), in this study a control measurement was included. For this study patients with chronic bronchitis with abundant sputum production were selected. The same type of patients were included in studies to evaluate the effect of oral high frequency oscillation (chapter V) and of several aerosols inhaled prior to a forced expiration technique session including postural drainage (chapter VI). In view of the increasing number of conflicting reports on patients with primary ciliary dyskinesia the study described in chapter VII reporting the results of the measurement of tracheobronchial clearance in patients with dextrocardia was performed. Efforts were made to correct for the effect of cough in order to determine the amount of effective mucociliary transport in these patients. Furthermore these patients and, in general, patients with the primary ciliary dyskinesia syndrome quite often receive chest physical therapy. The results described in chapter VII should add to the understanding of the efficacy of cough and/or physiotherapy in this kind of patients.

Patients with chronic bronchitis reported a subjective enhancement of expectoration during and directly after sauna to such an extend that it might even replace chest physical therapy. Therefore a study was undertaken to investigate the effect of sauna on tracheobronchial clearance in chronic bronchitics (chapter VIII).

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Chapter II

Variability of tracheobronchial clearance in healthy non-smoking subjects

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KEY WORDS: Variability; Reproducibility; Mucociliary clearance; Tracheobronchial clearance; Area under the curve

ABSTRACT

Tracheobronchial clearance was measured twice in 10 healthy non-smoking volunteers to evaluate inter- and intrasubject variability, using a radio-aerosol technique (5 μm ^{99m}Tc labelled polystyrene particles). By means of two detectors radioactivity in the lungs was measured at regular intervals for 6 hours and once more 24 hours after inhalation. The decrease in radioactivity after correction for background activity, isotope decay and 24-hour retention was assumed to reflect tracheobronchial clearance. Among other parameters to quantitate the results of these tests, the area under the retention curve up to 6 hours after inhalation (AUC-6) was calculated. The intersubject coefficient of variation (COV) using the AUC-6 was 31%. The intrasubject COV of the AUC-6 was 11%. These results compare favourably with those reported by others using different techniques. It is concluded that the intrasubject variability of tracheobronchial clearance as measured by this technique is small.

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Introduction

Several methods and techniques to measure tracheobronchial clearance have been described[1-5]. Only few studies have focused on the variability of the results of these measurements[6-11]. There is no study on the intrasubject variability in healthy subjects of tracheobronchial clearance as measured by means of the non-invasive radio-aerosol technique developed by Thomson and Short[4]. The aerosol which they used contained 5 μm tetraphenylarsonium pertechnetate labelled polystyrene particles. Polystyrene has the advantage of being biologically inert and non-hygroscopic as well in contrast to, for instance, albumin microspheres or erythrocytes. The procedure to label these particles with ^{99m}Tc results in a low leaching tendency, i.e. less than 5% in 24 hours[12].

In order to be able to evaluate the effects of various physiological factors and of medication on tracheobronchial clearance in healthy non-smokers, the inter- and intrasubject variability as measured by this technique, have to be known. Tracheobronchial clearance was therefore assessed on two occasions in healthy non-smoking volunteers.

Methods

The method used has been described by Thomson and Short[4]. ^{99m}Tc as tetraphenylarsonium pertechnetate was dissolved in a polystyrene solution consisting of xylene and methylisobutyl ketone. This solution was fed to a spinning top generator (R.E.May Spinning Top Aerosol Generator, Research Engineer Ltd) rotating at such a speed that droplets were produced which, after evaporation of the solvent, left 5 μm particles (GSD = 0.80). On average this solution contained 14 mCi (518 MBq). The aerosol was produced in a 90 litre airtight tank. The subjects inhaled from this tank, which was linked in series with a wet spirometer (Pulmotest-Godart), by which the average flow of the inhalations (i.e. volume inspired/time for inspiration) was registered and their volume controlled, aiming at 450-500 ml. After each inhalation there was a 3-second breathhold. The number of inhalations in each test varied, depending on the estimated concentration of radioactivity in the aerosol. After the inhalations were completed, the subject was instructed to gargle and rinse the mouth in order to remove activity deposited there.

Particle size, shape and presence of aggregates were checked regularly by examining slides left on the bottom of the aerosol tank, using a light microscope at a magnification up to 650 times.

The radioactivity in the thorax was measured by means of two horizontally opposed scintillation detectors (2 inch Thallium activated NaI crystals). One detector was placed in front of the seated subject and centred midway the sternum, and the other behind the subject and centred at the spinal column. Interference of activity present in stomach or throat with the measurement of activity present in the lungs was reduced to a minimum by using collimators with an aperture of 9.0 cm diameter at 2.5 cm from the crystal. Before each measurement the subject was asked to drink some water to remove radioactivity present in the oesophagus. The contours of the detectors were marked on the skin for reproducible repositioning. Radioactivity was measured for 90 seconds at regular intervals during 6 hours, starting immediately after inhalation. The number of measurements per test averaged 16. Radioactivity was measured for 5 minutes at 24 hours after inhalation. This measurement was supposed to be an estimate of radio-aerosol deposition in the non-ciliated regions of the lungs. The sum of the radioactivity counts of the two detectors was corrected for background activity, isotope decay and 24-hour retention. The tracheobronchial retention curve was obtained by expressing the corrected counts as percentage of the number of counts in the first measurement after inhalation and plotting that against time after inhalation. In every individual retention curve the percentages at each 20-minute interval were interpolated and used to calculate the mean of the tracheobronchial retention curves of the groups as a whole. The percentages of initial activity cleared at 2, 4 and 6 hours after inhalation of the radio-aerosol were also calculated by interpolation of the tracheobronchial retention curves. The area under the retention curve up to 2 (AUC-2), 4 (AUC-4) and 6 hours after inhalation (AUC-6) was calculated using non-fitted data and expressed in % hours.

Two-way analysis of variance (ANOVA) was applied to detect a systematic difference between the first and second test. One-way ANOVA was applied to evaluate intra- and intersubject variation for each method of clearance assessment. The results are expressed as coefficients of variation (COV).

Wilcoxon's test for paired data was used to evaluate the significance of any differences observed.

As described by Hills and Armitage[13] we calculated the number of subjects needed to be included in each limb of a cross-over design study, in order to detect given differences at $p < 0.05$ with various probabilities of success (power). For this the following formula was used: $n = (A^2 \times SD_d^2)/(2 \times D^2)$ where, A = (actual difference)/(standard error) varying for different powers; SD_d = standard deviation for the paired differences between the two measurements of the cross-over study; D = expected mean differences between the two measurements. The power of a trial is defined as the probability that the trial will produce a difference between treatments which is significantly different from zero at a certain statistical level of significance (usually taken to be 5%)[13].

Since the cross-over study design usually consists of two limbs the total number of patients necessary for such a study was taken as twice that given by the above formula, i.e. 2n.

The tracheobronchial clearance was measured twice under identical conditions. In order to avoid possible diurnal variation in each subject tracheobronchial clearance was measured at the same time of the day. The median interval between the two tests was 13 days, ranging from 7 to 210 days.

Subjects

Ten healthy non-smoking male volunteers took part in the study. Individual data are listed in Table 1. They did not take any medication. There was no history of recent respiratory tract infection.

Lung function tests were performed in all subjects. Results are listed in Table 1. The mean ratio $FEV_1/FVC\%$ was 82%, which was 106% of the predicted value.

The subjects were informed about the design and the aims of the study. Written informed consent was obtained.

The study was approved by the Medical Ethics Committee of the hospital.

Results

Data concerning the inhalations are listed in Table 1. In two subjects the amount of inhaled radioactivity was measured by means of a whole body counter and appeared to be 0.02 mCi (740 kBq). The estimated effective dose equivalent was 0.09 mSv (= 9 mrem).

Table 1. Data on age and lung function of the subjects, flow and volume of the radio-aerosol inhalations, and 24-hour retention.

Subject	Age	Lung function % predicted FVC	Lung function % predicted FEV[1]	Inhalation mean volume ml I	Inhalation mean volume ml II	Inhalation mean flow l/min I	Inhalation mean flow l/min II	24-hour retention (% initial activity) I	24-hour retention (% initial activity) II
1	46	119	125	454	488	28	37	67	67
2	31	119	120	439	468	62	65	54	58
3	24	81	98	480	532	67	78	46	48
4	22	114	124	570	508	62	76	66	55
5	23	100	103	496	488	65	79	38	49
6	25	99	105	560	595	87	91	45	36
7	22	97	97	456	505	59	75	46	33
8	22	125	120	442	463	60	-*	60	53
9	26	115	125	442	462	47	50	53	59
10	27	109	120	477	463	47	44	58	55
Mean	27	108	114	482	497	58	66	53	51
SD	-	13	12	48	42	15	18	10	10

I = first measurement
II = second measurement
* = flow not recorded due to malfunction of spirometer

The mean of the tracheobronchial retention curves of the first and the second test of all subjects is presented in Figure 1. Statistical analysis of these two curves revealed no significant difference.

Two-way ANOVA of the percentages activity cleared and the areas under the retention curve revealed no systematic difference between the first and second test (p-value ≥ 0.25). The clearance of radioactivity expressed as percentage of the initial amount of radio-activity cleared 2 (2h), 4 (4h), and 6 hours after inhalation (6h) in the first (I) and the second test (II), was calculated and is listed in Table 2, including the intersubject COV for 2,4 and 6 h % clearance. The mean of the intersubject COV of the first and the second test of 2 h% clearance was 44%. The intrasubject COV of this parameter was 15%. For 4 h % clearance these figures were 21% and 11% respectively, and for 6 h% clearance 12% and 5% respectively.

The percentages of initial activity present 24 hours after inhalation of each test are listed in Table 1. Flow and 24-hour retention were negatively correlated ($r = -0.70$; $p < 0.001$) (see also Figure 2).

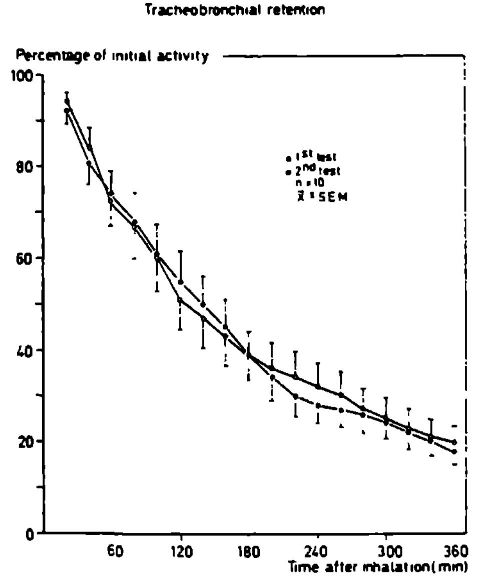

Figure 1. The mean of the tracheobronchial retention curves of the first and the second test.

Table 2. Clearance of radioactivity expressed as percentage of the initial amount of radioactivity cleared at 2 (2h), 4 (4h), and 6 hours after inhalation (6 h) in the first (I) and the second test (II).

Subject No.	2 h, % I	2 h, % II	4 h, % I	4 h, % II	6 h, % I	6 h, % II
1	48	45	60	85	83	90
2	53	45	72	75	85	85
3	41	37	82	73	85	80
4	39	49	67	63	80	74
5	62	62	78	80	83	90
6	67	47	75	80	88	90
7	90	90	95	95	95	92
8	15	30	37	57	62	60
9	29	14	55	58	73	84
10	44	42	62	58	69	76
Mean	49	45	68	72	80	82
SD	21	20	16	13	10	10
COV*	43	44	24	18	12	12

*COV = intersubject coefficient of variation.

Figure 3 shows the results of the calculated area under the retention curve up to 2 (AUC-2), 4 (AUC-4) and 6 hours after inhalation (AUC-6) in the first and the second test.

The intrasubject COV of the AUC-2, the AUC-4 and the AUC-6 were 9%, 9% and 11% respectively. The mean of the intersubject COV of the AUC-2 was 20%. For the AUC-4 and AUC-6 this was 28% and 31% respectively.

In table 3 are presented the numbers of subjects required to be entered into a cross-over study in order to detect given differences in the 2, 4 and 6 h% clearance or AUC-2, 4 and 6, with various probabilities of success at $p < 0.05$.

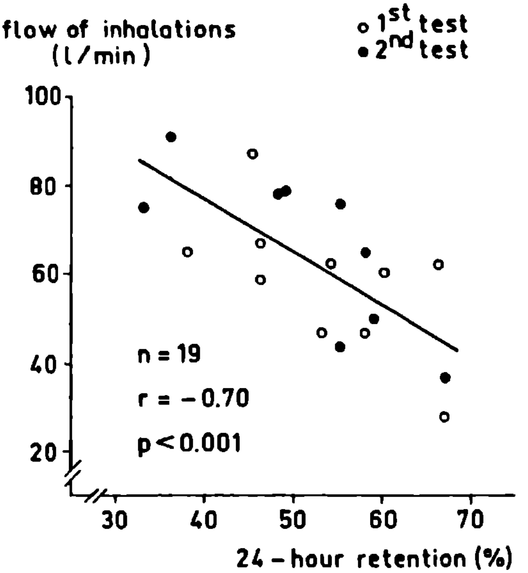

Figure 2. Relation between the average flow of the inhalation and the 24-hour retention.

Table 3. Number of subjects needed to be entered in a cross-over study in order to detect given absolute differences in 2, 4 and 6 h% clearance or area under the tracheobronchial retention curve up to 2 (AUC-2), 4 (AUC-4) and 6 hours after inhalation (AUC-6) at $p < 0.05$ with various probabilities of succes (power).

clearance		Power (%)						AUC	
(%)		70	75	80	70	75	80	(% hrs)	
2 h	5	26	30	33	6	7	8	20	AUC-2
	10	7	8	8	2	2	2	35	
	15	3	3	4	1	1	1	50	
	20	2	2	2	1	1	1	70	
4 h	5	28	31	35	16	18	20	20	AUC-4
	10	7	8	9	5	6	7	35	
	15	3	4	4	3	3	3	50	
	20	2	2	2	1	2	2	70	
6 h	5	9	10	11	30	35	39	20	AUC-6
	10	2	3	3	10	11	13	35	
	15	1	1	1	5	6	6	50	
	20	1	1	1	3	3	3	70	

Discussion

This study was performed to evaluate inter- and intrasubject variability of the tracheobronchial clearance as measured using the technique described by Thomson and Short[4].

The clearance rate is influenced by the deposition pattern[14]. The deposition itself depends on particle size, mode of inhalation and airway patency. The spinning top generator produces a monodisperse aerosol. The volume and the flow of the inhalations in each subject were similar in the first and second test (see Table 1). In healthy non-smokers airway patency should not be a factor. The resulting 24-hour retention was not significantly different in the two tests. It is assumed that 24-hour retention is equivalent to alveolar deposition[15], or rather: deposition in the non-ciliated regions of the lungs. The negative correlation between flow of inhalation and 24-hour deposition is therefore as to be expected. Even at this flow, and while rebreathing of particles was prevented by means of a one-way valve system, there was a significant deposition of 5 μm particles in the most distal regions of the lung in these healthy subjects. The mean 24-hour retention in our study was 52%. Using the same technique Agnew et al found a mean 24-hour retention of 41% at a mean inspiratory flow of 49 l/min in 9 non-smoking volunteers[14]. The mechanical properties of the lung are known to change with age, but the relation between age and aerosol deposition is not certain. Because data on the age of the subjects in the study of Agnew et al are not available, it remains questionable whether the results of their study can be compared with our results.

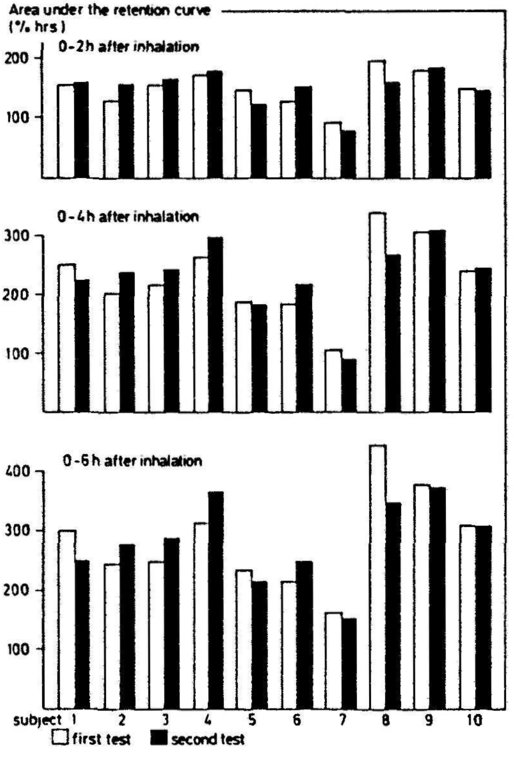

Figure 3. The area under the retention curve up to 2 (AUC-2), 4 (AUC-4), and 6 hours after inhalation (AUC-6) in the first and the second test of all subjects.

Using a 5 μm polystyrene aerosol also, Thomson and Short found in 3 non-smoking healthy volunteers with a mean age of 56 years a mean 24-hour retention of 42%[4]. The volume of the inhalations was 110 ml. The flow of the inhalations is not mentioned.

Camner and Philipson reported a mean alveolar deposition of 52% in 10 healthy volunteers measured on two occasions[16]. The test aerosol contained 4 μm teflon particles tagged with ^{111}In. These subjects performed 20-30 maximum inhalations at a 30 l/min rate. Their mean age was 27 years.

Booker et al used a 5 μm ^{51}Cr (half-life 28 days) labelled polystyrene aerosol in 3 subjects[15]. After a single 500 ml inhalation at normal breathing level followed by a 10 second breath-holding pause, they found an alveolar deposition of 75, 65 and 75%. Stahlhofen et al found in 5 healthy non-smoking subjects a mean 24-hour retention of 74%[17]. The age of these subjects ranged from 40 to 50 years. The radio-aerosol contained teflon particles with an aerodynamic diameter of 4.7 micrometer. The aerosol was inhaled at a flow rate of 15 l/min and an inspiration time of 4 seconds.

In another study by Stahlhofen et al, dealing with particle deposition in relation to particle diameter and flow of inhalation, alveolar deposition of 5 μm particles appeared to be 65% at a 45 l/min and 79% at a 15 l/min flow rate[18]. Deposition was measured several times in 3 healthy non-smoking subjects while the particle diameter was varied. The aerodynamic particle diameter ranged from 1 to 10 micrometer. The test aerosol contained iron oxide particles tagged with ^{198}Au.

Finally our results are in agreement with the model for aerosol deposition of the Task group on Lung Dynamics, which assumes tracheobronchial and alveolar deposition of 5 μm particles to be equal[19]. The discrepancies between the reported deposition patterns may have been due to type, number, positioning and collimation of the detectors used. Apart from the study by Agnew et al[14] the set-up to measure intrathoracic activity in our study was different from every other study mentioned above. It is obvious, however, that the results of measuring the 24-hour retention in our study appear to be not so astonishing in view of the literature.

There are several methods to quantitate the results of tracheobronchial clearance measurements[20]. The AUC-6 comprises the results of the measurements of the whole period during which most of the clearance is completed. This parameter is therefore likely to be the most sensitive with respect to detecting overall effects of different interventions.

In table 4 coefficients of variation for various measurements of tracheobronchial clearance reported in other studies and this study are listed. Our results compare favourably with those reported in other studies.

In table 3 the results are listed of the calculation of the number of subjects needed to be entered in a cross-over study in order to detect given absolute differences with various probabilities of success. It seems obvious that as the absolute differences to be detected are smaller the number of subjects needed does increase. Also a higher probability of success requires a larger number of subjects. We deliberately have chosen several absolute differences and powers identical to those listed in the study of Del Donno et al.[11] to be able to compare their results with those of our study. The numbers of healthy non-smoking subjects needed to be entered in cross-over studies as based on the results of our study are far lower than the numbers of chronic bronchitic or asthmatic patients mentioned in their study[11]. The rather small number of subjects required for detecting differences in 6 h% clearance seems to be remarkable. It must be explained by the fact that in healthy subjects tracheobronchial clearance is practically completed in 6 hours resulting in little variation in 6 h% clearance values. Looking at the numbers of subjects needed to detect differences in area under the retention curve it must be noted that, as

Table 4. Coefficients of variation for various measurements of tracheobronchial clearance. Comparison of our results with those reported by other studies including healthy non-smokers.

	Number of subjects	Type of measurements	Intrasubject COV (%)	Intersubject COV (%)
Puchelle et al. (8)	16	1h %TBC	16	42
Yeates et al. (10)	22	2h %TBC	20	43
Our study	10	2h %TBC	15	44
Wilkey et al. (9)	9	2h %TBR	14	35*
Our study	10	4h %TBC	11	21
Wilkey et al. (9)	9	4h %TBR	29	45*
Our study	10	6h %TBC	5	12
Our study	10	AUC-2	9	20
Our study	10	AUC-4	9	28
Our study	10	AUC-6	11	31
Camner et al. (7)	8	biological $t_{½}$	25	76*

2h, 4h, 6h %TBC: % of tracheobronchial deposition cleared at 2, 4 and 6 hours after radio-aerosol inhalation; 2h, 4h %TBR: % of tracheobronchial deposition present at 2 and 4 hours after radio-aerosol inhalation; biological $t_{½}$: biological half-lives extrapolated from the clearance curves. AUC-2, 4 and 6: area under tracheobronchial retention curve up to 2, 4 and 6 hours after radio-aerosol inhalation.
* derived from published data.

mentioned above, the AUC comprises all measurements during a whole period. Therefore the longer the period the larger the differences inevitably will be. A certain absolute difference in, for instance, AUC-2 is therefore comparable only with a larger absolute difference in, for instance, AUC-6.

It is obvious that in order to determine the number of subjects needed to be entered in a cross-over trial, it has to be decided first which difference is considered as being clinically relevant.

On the basis of the results of this study it can be concluded, that tracheobronchial clearance in healthy non-smoking subjects has considerable intersubject variability but also there is far less intrasubject variability, which is in agreement with other studies[7-11].

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Chapter III

Conventional physiotherapy and forced expiration manoeuvres have similar effects on tracheobronchial clearance

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KEYWORDS: Forced expiration technique; percussion; physiotherapy; postural drainage; regional clearance; tracheobronchial clearance.

ABSTRACT

This study compared the effect of two forms of chest physiotherapy. In the 'conventional' form of physiotherapy, postural drainage was combined with percussion and directed coughing. The other, relatively new form of physiotherapy, was the forced expiration technique, *i.e.* huffing combined with postural drainage, breathing exercises and, if necessary, coughing. Eight patients (six with cystic fibrosis, two with agammaglobulinaemia) took part in the study. No difference was found in tracheobronchial clearance, regional lung clearance, sputum production or lung function between the two forms of treatment. The forced expiration technique can be performed without an assistant. Therefore, it is concluded that in general the forced expiration technique is preferable.

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Several techniques of chest physiotherapy have been developed in order to improve mucus mobilization in patients with retention of bronchial secretions.

Two frequently used regimens are conventional physiotherapy (CONV) and the relatively new forced expiration technique in combination with postural drainage (FET). CONV usually implies the combination of percussion and/or vibration with postural drainage and directed coughing. FET consists of huffing and breathing exercises combined with postural drainage and can be performed without an assistant.

By means of various non-invasive techniques using radionuclides, the effect of components of these regimens on mucus clearance have been evaluated separately and in combination with each other[1-8]. In contrast with the study by Oldenburg *et al.*[1], other studies have shown that postural drainage enhances tracheobronchial clearance[2-4]. Percussion and vibration have appeared to be relatively ineffective[5-6] and do not seem to add to the effectiveness of the combination of coughing, breathing exercises and postural drainage[7]. FET, even without postural drainage, enhances tracheobronchial clearance[8].

To our knowledge, no study has compared the effectiveness of conventional physiotherapy with that of the FET, both including postural drainage, using the objective *in vivo* assessment of tracheobonchial clearance by means of a radio-aerosol technique. The aim of this study was to compare the effect on tracheobronchial clearance and regional lung clearance of conventional physiotherapy with that of the forced expiration technique.

Methods

Patients

Six patients with cystic fibrosis and two with agammaglobulinaemia took part in the study. Their mean age was 23 yrs (range 15-27 yrs). The mean forced expiratory volume in one second (FEV_1) was 65 (SD ± 29)% predicted. The mean vital capacity (VC) was 80 (SD ± 19)% predicted. The mean sputum production was 53 g per day.

Study design

In order to standardize the treatment as much as possible only two experienced physiotherapists participated. The duration of a CONV- or FET-session was 30 min.

Both regimens included postural drainage consisting of six positions, four lying on a tilted bed (15° head down) and two seated (leaning 45° forward and 30° backwards, respectively). During CONV, in each position, percussion was applied for 4 min followed by a few deep breaths and directed coughing. FET was applied according to standard procedures[9]. During FET, in every postural drainage position, the patients were instructed to start with diaphragmatic breathing. When the patient had relaxed sufficiently this was followed by thoracic expansion exercises and again diaphragmatic breathing. Then followed two huffs (maximal forced expirations from mid-lung volume) with chest compression alternated with relaxed diaphragmatic breathing. If necessary the patients coughed. FET was performed without aid. The protocols of CONV and FET were similar to the regimens in clinical practice. There was a four-day treatment period in a randomized order for both CONV and FET. The first three days were used for daily instruction and treatment of the patients. On the fourth day the effect of the respective treatments was assessed. Medication was continued unaltered during the study. The clinical condition of the patients had to be stable for at least six weeks prior to and during the study period.

The patients were informed about the design and the aims of the study. Written informed consent was obtained. The study was approved by the Medical Ethics Committee of the hospital.

Test parameters

Tracheobronchial clearance was measured using a radio-aerosol technique[10]. A monodispersed 5 μm ^{99m}Tc-labelled polystyrene particle aerosol was inhaled under standardized conditions.

The radioactivity in the thorax was measured by means of two horizontally opposed scintillation detectors. One detector was placed in front of the seated subject and centred at the sternum, and the other behind the subject and centred at the spinal column. Measurements were started directly after inhalation and repeated at regular intervals, *i.e.* approximately every 20 min up to 2,5h after physiotherapy was started and once more at 24h after inhalation. As described by Pavia *et al.*[11], the sum of the radioactivity count rates of the two detectors was corrected for background activity, isotope decay and 24h retention. The latter is considered to be an estimate of the aerosol deposition in the non-ciliated regions of the lung. The corrected count rate was expressed as a percentage of the count rate assessed immediately before the start of the physiotherapy. These percentages were plotted against time after the start of the physiotherapy, thus resulting in tracheobronchial clearance curves. The mean of the eight individual clearance curves obtained during either CONV or FET was calculated using the values actually measured at 20 min intervals. In the case of different intervals interpolations were made.

Regional lung clearance was estimated by means of gamma-camera imaging as described by Agnew *et al.*[12] with the exception of correction for alveolar depostion.

A posterior 40,000-count image was recorded directly before and after each therapy session. Each subject also had a 200,000-count posterior ventilation study using radioactive krypton (^{81m}Kr). The gamma-camera images were recorded in 64x64 format with a MDS computer system (MDS-A^2, Medtronic Medical Data Systems, Ann Arbor, Michigan, USA).

By means of the contours of the ^{81m}Kr image a 5x8 matrix was fitted on each lung. The lungs were thereby divided into inner, intermediate and peripheral zones (fig. 1). Regional clearance after physiotherapy was expressed as a percentage of the count rate in a particular zone before the treatment plus the commulative loss of count rate from more peripheral zone(s).

Sputum was collected during the physiotherapy session and during the 24h following the radio-aerosol inhalation. Sputum wet weight was recorded. In addition sputum was dried for 72h at 50°C to determine sputum dry weight.

Flow volume curves were measured just before radio-aerosol inhalation and at about 90 min after physiotherapy.

The Wilcoxon test for paired data was used to evaluate the significance of any differences observed.

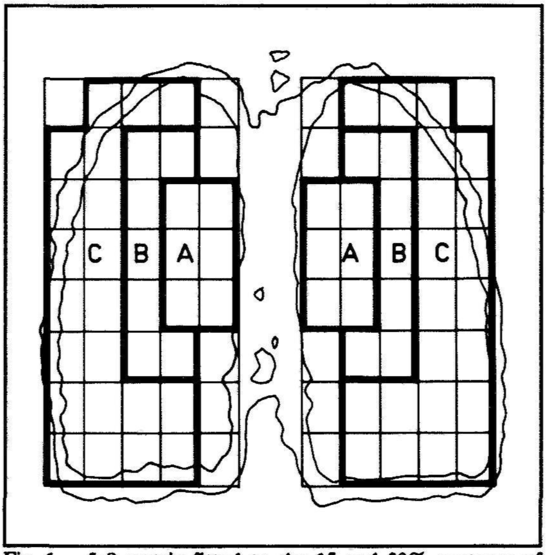

Fig. 1. – 5x8 matrix fitted to the 15 and 30% contours of the ^{81m}Kr ventilation image. A: inner zone; B: intermediate zone; C: peripheral zone.

Results

No significant difference between 24h retention after CONV and after FET was found. The mean 24h retention was 42 (SD ± 12)% and 38 (SD ± 15)%, respectively.

The mean curves of the tracheobronchial clearance obtained during CONV and FET are presented in figure 2. At every interval there appeared to be no significant difference between the two curves. The results of the measurement of regional lung clearance are shown in figure 3. Again no significant differences were found between CONV and FET.

The mean sputum production during the treatment was 754 mg (SD ± 733) dry weight for FET. The mean 24h sputum production was 51 g (SD ± 52) wet weight for CONV and 55 g (SD ± 58) wet weight for FET.

The mean values for FEV_1 and forced vital capacity (FVC) before and after CONV and FET, respectively, are listed in table 1. There was no change in lung function after physiotherapy nor were there significant differences between CONV and FET.

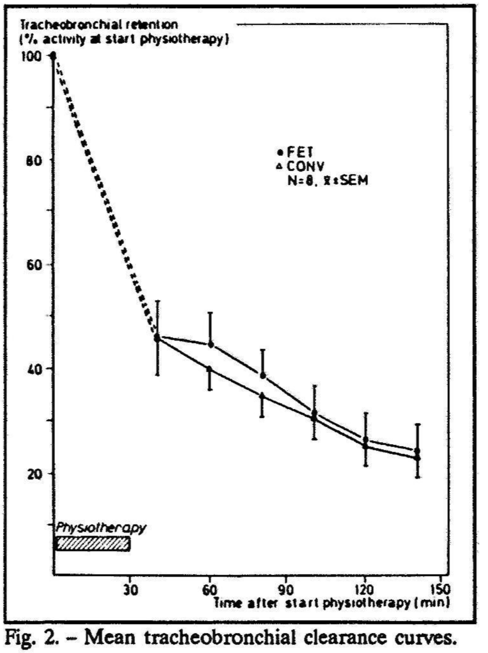

Fig. 2. – Mean tracheobronchial clearance curves.

Table 1. – Lung function data (n=8).

	before	after	before	after
	CONV		FET	
Mean FEV_1 *l*	2.3	2.4	2.3	23
Mean FVC *l*	3.5	3.7	3.7	37

There appeared to be no correlation between the amount of 24h sputum production and the effect of either treatment on tracheobronchial clearance or regional lung clearance, nor between the degree of airway obstruction and clearance.

Discussion

Bateman *et al.*[13] described the effectiveness of the combination of percussion, vibration and postural drainage compared to control. Sutton *et al.*[8] demonstrated the effect of FET alone and combined with postural drainage compared to control[9]. The radio-aerosol technique, which has been used to measure tracheobronchial clearance in both these studies, is identical to the technique used in our study. Since the efficacy of both CONV and FET had been proven in the two studies mentioned above, no control measurement was included in our study.

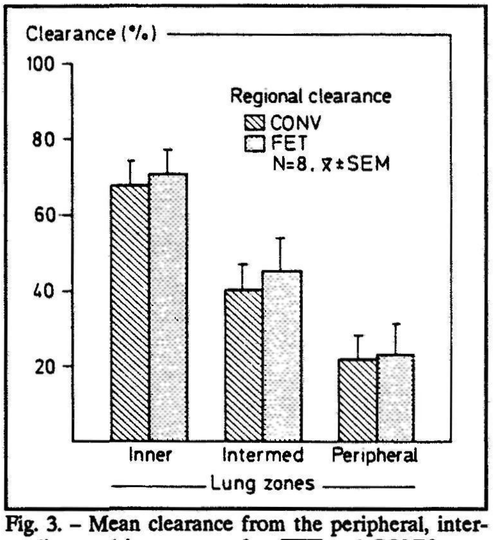

Fig. 3. – Mean clearance from the peripheral, intermediate and inner zone after FET and CONV.

The design of the study and the protocols of the two treatments were such, that the common practice of the patients requiring daily chest physiotherapy was mimicked as closely as possible. The results of this study are therefore, directly applicable to the treatment of these patients. However, the design of the study, *i.e.* three days with optimal chest physiotherapy whilst effects were evaluated on the fourth day, may have had a negative effect on the discriminative power of the study.

In our study no significant difference was found between the two treatments, which both included postural drainage. Therefore, the question arises whether the addition of other techniques (percussion, FET) substantially increases the effect of postural drainage. In several studies[5-7] no additional effect of percussion has been shown. Furthermore, chest physiotherapy consisting of postural drainage in several postions during one session, including percussion, has been shown to produce a fall in oxygen saturation[14]. A more recent study[15] showed a fall in oxygen saturation particularly related to chest percussion. The forced expiration technique appeared to increase the efficacy of postural drainage[8]. After proper instruction and training practically every patient can perform the forced expiration technique without assistance. Patients, who require regular physiotherapy, therefore become more independent. It is important to prevent physiotherapist dependency in these patients. Independence also reduces expense related to treatment by a physiotherapist. Despite this and the fact that the value of percussion and vibration still remains to be proven, many doctors and physiotherapists, as well as patients, seem to be reluctant to switch from conventional physiotherapy to the forced expiration technique.

On the basis of the results of this study it can be concluded that the forced expiration technique, including postural drainage, is as effective as conventional physiotherapy. In view of the considerations mentioned above the forced expiration technique is preferable, especially for long-term treatment.

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RÉSUMÉ: Cette étude compare les effets de deux formes de physiothérapie thoracique. Dans la forme 'conventionnelle', on a combiné le drainage postural avec la percussion et la toux dirigée. L'autre forme, relativement nouvelle, de physiothérapie, consiste en une technique d'expiration forcée, avec halèment, drainage postural, exercises repiratoires, et toux en cas de nécessité. 8 patients ont participé à l'étude (6 cas de fibrose kystique, 2 cas d'agammaglobulinémie). On n'a pas trouvé de différence entre les deux techniques en ce qui concerne la clearance trachéo-bronchique, la clearance pulmonaire régionale, la production d'expectorations, ou les épreuves fonctionnelles pulmonaires. La technique d'expiration forcée peut être réalisée sans assistance. C'est la raison pour laquelle on conclut qu'en général il y a lieu de préférer cette dernière technique.

Chapter IV

IV.1 The effect of positive expiratory pressure versus forced expiration technique on tracheobronchial clearance in chronic bronchitics

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KEYWORDS: Forced expiration technique; physical therapy; positive expiratory pressure; tracheobronchial clearance

ABSTRACT

In a randomized cross-over trial, including a control measurement the effect of positive expiratory pressure (PEP) and forced expiration technique (FET) on tracheobronchial clearance was evaluated in eight chronic bronchitics with abundant sputum production (mean, 32 g/day). PEP consisted of PEP-mask breathing interspersed with breathing exercises, huffing, and coughing. FET consisted of postural drainage, breathing exercises, huffing, and coughing. Clearance was measured with a radio-aerosol technique. At 40 min after the start of therapy the mean clearance, expressed as percentage of the amount of radioactivity present at the start of therapy, was 32% after PEP, 53% after FET, and 15% in the control run. The difference between PEP, FET, and control was statistically significant ($p<0.02$). Sputum production during PEP and FET was larger than during the equivalent period of time in the control run. It is concluded that FET is more effective than PEP in enhancing tracheobronchial clearance.

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Positive expiratory pressure (PEP) breathing is thought to mobilize secretions in occluded airways by increasing collateral ventilation[1]. Recently, the beneficial effect of positive airway pressure by mask has been reported in the treatment of surgical patients with atelectasis[2]. Since then, there have been several other studies on the clinical effects of PEP. Enhancement in sputum production[3,4] and improvement in lung function variables[3,5,6] have been described. In a recent study PEP was found to have no effect on clinical variables[7]. The lack of consistency in the results of these studies could be due to the choice of factors. The measurement of tracheobronchial clearance with a non-invasive radio-aerosol technique is an objective in-vivo assessment of the effect of chest physiotherapy[8]. By this technique the efficacy of the forced expiration technique (FET), especially when combined with postural drainage, has been demonstrated[9]. No study dealing with PEP has used the measurement of tracheobronchial clearance.

The aim of this study was to assess the effect of PEP-mask physiotherapy on tracheobronchial clearance as compared with the forced expiration technique in patients with chronic bronchitis. Furthermore, lung function and sputum production were measured.

Patients and methods

Eight patients (seven male, one female) with chronic bronchitis as defined in accordance with the MRC criteria[10] took part in the study.

The mean age of the patients was 63 (range, 48-73) years. The mean forced expiratory volume (FEV_1) was 1.79 l (SD ± 0.65 l); the mean forced vital capacity (FVC), 3.07 l (SD ± 1.07 l); and the mean FEV_1/VC was 49 (SD ± 15)% – that is, 64% of predicted. The mean sputum production was 32 (range, 16-58) g/day.

If medication was taken, this was continued unchanged during the study.

In each patient tracheobronchial clearance was measured three times (PEP, FET, and control) on separate days with at least 2 days in between. The sequence of the measurements in each patient was determined at random. Several days before each measurement the patients were made familiar with the use of the PEP-mask and the forced expiration technique during at least three separate sessions. On the 2 days directly before each measurement no physiotherapy at all was allowed.

The protocol of a PEP session included PEP-mask (Astra-Meditec, the Netherlands) breathing for 2 min at a PEP level of 10-15 cm H_2O, sitting with the elbows resting on a table, followed by a few cycles of abdominal breathing, after which the patient performed a few huffs (forced expirations from mid-lung volume). Mobilized secretions reaching the central airways were cleared by coughing. This procedure was performed five times, resulting in a total duration of about 20 min. The FET-session protocol included six positions of postural drainage, of which four were in the Trendelenburg position. In each position the patient started with relaxed abdominal breathing, followed by thoracic expansion exercises. After that the patient resumed relaxed abdominal breathing interspersed each time with a few huffs (maximum 3). Secretions in the central airways, if present, were expectorated. The duration of a

FET session was about 30 min. During the control measurement the patient had no physiotherapy and coughed only spontaneously.

The variables in this study included tracheobronchial clearance, lung function, and sputum production.

Tracheobronchial clearance was measured with a radio-aerosol technique[11]. A monodisperse 5-μm ^{99m}Tc-labelled polystyrene particle aerosol was inhaled from a 90-l air-tight tank. This tank was linked in series with a wet spirometer (Pulmotest, Godart) by which the flow of the inhalations was registered and their volume controlled, aiming at 400-500 ml. For each test this volume was inhaled 15 times. Physiotherapy was not started until 40 min after inhalation of the tracer, to avoid the most rapid clearance phase. The radioactivity in the thorax was measured by means of two horizontally opposed scintillation detectors (5-cm thallium-activated NaI crystals). One detector was placed in front of the seated patient and centred midway on the sternum. and the other was placed behind the patient and centred at the spinal column. Radioactivity was measured during 90 sec at regular intervals up to 2.5h after the physiotherapy was started and once more 24h after inhalation, because the latter is supposed to be an estimate of radio-aerosol deposition in the non-ciliated regions of the lungs. In four patients one more measurement was performed about 7h after inhalation. The sum of radioactivity count rates of the two detectors was corrected for background activity, isotope decay, and 24-h retention.

These corrected count rates were expressed as a percentage of the count rate assessed immediately before the start of physiotherapy. These data were plotted against time after the start of physiotherapy, resulting in tracheobronchial clearance curves. The mean of the eight individual clearance curves obtained during either PEP, FET, or control was calculated by using the interpolated percentages at 20-min intervals. The area under the clearance curve of each individual measurement was calculated by using non-fitted data and expresed in arbitrary units (hours).

Lung function was measured just before inhalation of the radio-aerosol and about 1.5h after physiotherapy, including a flow volume curve and sGaw by means of a body plethysmograph (Jaeger Bodyscreen II).

Sputum production during PEP, FET, and control periods and during the remainder of the day of measurement was recorded by weighing the sputum samples. The macromolecular content of the sputum samples was determined by weighing them after drying for 3 days at 50°C.

Wilcoxon's test for paired data was used to evaluate the significance of any differences observed.

Written informed consent was obtained from each patient. The study was approved by the Medical Ethics Committee of the hospital.

Results

The data on the 24-h retention of radioactivity are presented in Table 1. No significant differences were found.

Table 1. – Data on tracheobronchial retention (mean±SD, n=8).

	PEP	FET	Control
24-h retention (% initial deposition)	34 ± 16	31 ± 10	36 ± 18
Retention after therapy‡	70 ± 14*	46 ± 15†	86 ± 16
AUC 150§ (h)	167 ± 26*	120 ± 28†	192 ± 39

* $p<0.05$ as compared with control; † $p<0.02$ as compared with PEP and control; ‡ Percentage of radioactivity present at start of physiotherapy; § AUC 150 = aria under the clearance curve 0-150 min after the start of physiotherapy.

The mean curves of the tracheobronchial clearance obtained during and after PEP, FET, and control are presented in Fig. 1. At 20 and 40 min there is a significant difference between control and PEP ($p<0.02$). The FET curve was significantly different from the control curve at each 20-min interval ($p<0.02$) but not at the 20-min value.

The data on tracheobronchial retention after physiotherapy are shown in Table 1.

Table 1 also presents data on the mean area under the clearance curve up to 150 min after the start of physiotherapy (AUC 150). Tracheobronchial retention at 7h after inhalation of the radio-aerosol was measured in four patients. The mean percentages were 20

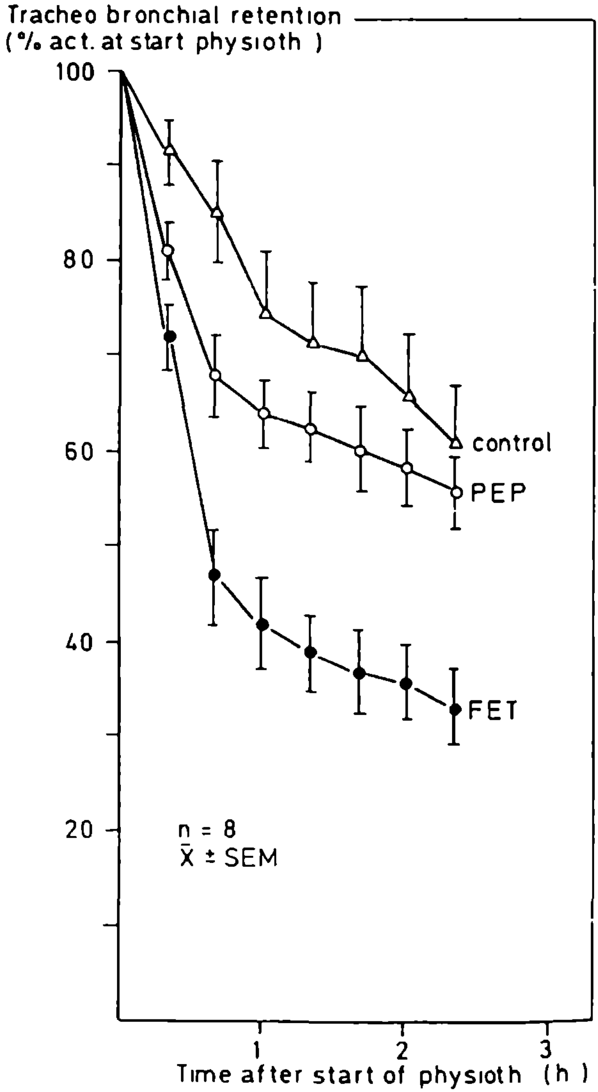

Fig. 1. – The mean of the tracheobronchial clearance curves for PEP, FET, and control.

± 7%, 13 ± 8%, and 24 ± 24% for PEP, FET, and control, respectively. These results showed no significant differences.

Lung function variables as measured before and after either of the treatments and control period were not significantly different (Table 2).

Both for PEP and FET significantly more sputum was produced during physiotherapy than during the equivalent period of time in the control measurement ($p<0.02$) (Table 3).

During FET more sputum was produced than during PEP ($p<0.05$). Sputum production during the 2h after therapy was the same for FET and PEP. The mean daily sputum production for FET, PEP, and control was not significantly different.

Table 2. – Lung function data before and after therapy ($n=8$).

	PEP		FET		Control	
	Before	After	Before	After	Before	After
Mean FEV_1	1.9	1.8	1.7	1.7	1.8	1.7 l
SD	0.7	0.6	0.6	0.5	0.6	0.5 l
Mean FVC	3.2	3.3	3.0	3.0	3.0	3.1 l
SD	1.0	1.0	1.0	0.9	0.9	0.9 l
Mean sGaw†	0.67	0.64	0.63	0.69	0.66	0.61*
SD	0.25	0.24	0.21	0.27	0.26	0.28*
Mean FEF_{25-75}‡	1.17	1.00	1.11	1.04	1.13	0.981sec
SD	0.48	0.42	0.45	0.36	0.45	0.421/sec

* 1/sec·kPa.

† sGaw = specific airway conductance.

FEF_{25-75}‡ = mean forced expiratory flow during the middele half of the FVC.

Table 3. – Data on sputum production (mean ± SD, $n=8$).

	PEP	FET	Control
During physiotherapy	59 ± 57*	249 ± 359 †	18 ± 32 mg dry weight
After physiotherapy (2 h)	55 ± 104	55 ± 55	83 ± 131 mg dry weight
24-h production	29 ± 10	37 ± 13	31 ± 11g wet weight

* $p<0.02$ as compared with control.

† $p<0.05$ as compared with PEP and $p<0.02$ as compared with control.

Discussion

The aim of the study was to compare the effect on tracheobronchial clearance of PEP-mask physiotherapy with that of the forced expiration technique in patients with chronic bronchitis and abundant sputum production.

The resulta of this study as expressed by the area under the clearance curve (AUC 150) indicate that both PEP and FET have a positive effect on tracheobronchial clearance compared with control. Analysis of the clearance curves shows that the effect of PEP is restricted to the period during and immediately after the treatment. After FET clearance is significantly more effective compared with both PEP and control even up to 2.5h after start of physiotheray.

It has been suggested that PEP particularly enhances the clearance of secretion in small airways[4]. Therefore one should expect the effect to manifest itself not directly after the treatment but after some hours. To detect these effects additional measurements were performed in four patients 7h after inhalation. Our data show no change in the differences between PEP, FET, and control already present at 2.5h after start of therapy. This provides no support for the idea that PEP has delayed effects.

For each treatment modality lung function variables, both for large and small airways, before and 1.5h after each single session, did not change significantly. The postulated delayed effect of PEP could not be detected by using these lung function variables also.

FET resulted in the largest sputum production during the treatment. The data on sputum production during the 2h after physiotherapy again show no evidence of a delayed effect of PEP.

The design of the study allows no conclusions with regard to the effect of PEP-mask breathing alone, because PEP included huffing and coughing, whereas in the control measurement patients coughed only spontaneously.

Both PEP and FET as used in this study enhanced tracheobronchial clearance. But FET was more effective than PEP. One of the reasons could be that postural drainage was not included in PEP. The importance of postural drainage also in combination with PEP has been demonstrated in a recent study[7]. The recommendations of the manufacturer seem therefore to be inadequate.

We conclude that the forced expiration technique including postural drainage is more effective than positive expiratory pressure physiotherapy in patients with chronic bronchitis and abundant sputum production.

Acknowledgement

The PEP masks used in this study were kindly supplied by Astra-Meditec, The Netherlands.

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IV. 2 The effect of positive expiratory pressure mask physiotherapy (PEP) versus forced expiration technique (FET) on regional lung clearance in chronic bronchitics

Running title: Effect of PEP on regional lung clearance

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ABSTRACT

On theoretical grounds it is assumed that positive expiratory pressure mask physiotherapy (PEP) as a means of promoting mucus clearance is especially effective in the more distal airways. In a randomized cross-over trial including a control measurement the effect of PEP and of the forced expiration technique (FET) which was combined with postural drainage (PD) on regional lung clearance was evaluated in seven patients with chronic bronchitis and abundant sputum production (mean 32 g/day). PEP consisted of positive expiratory pressure mask breathing interspersed with breathing exercises, forced expiration manoeuvres (huffing) and if necessary coughing. FET consisted of breathing exercises, huffing and also if necessary coughing. FET was combined with PD. Following inhalation of a radio-aerosol regional lung clearance was estimated by means of gamma camera imaging. The results after PEP appeared to be not significantly different from control. The mean clearance in all three lung zones (peripheral, intermediate and inner) was largest after FET with PD as compared with PEP and control. Statistical significance ($p \leq 0.02$) was reached only for clearance in the inner region. It is concluded that PEP has no demonstrable effect on regional lung clearance in these patients.

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Introduction

It has been reported by Falk et al.[1] that positive expiratory pressure mask physiotherapy (PEP), which is performed in a sitting position only, is better accepted than other forms of chest physical therapy, which do include postural drainage. Most patients find it easier, less time consuming and more convenient because they can use it whenever necessary.

PEP is thought to achieve its effect on mucus mobilization by increasing collateral ventilation[2], thereby opening up airways occluded by secretions and also by preventing airway collapse during expiration in obstructive lung disease[3]. It is assumed therefore that the effect of PEP on the mobilization of secretions in the peripheral airways is more pronounced than for instance the effect of coughing and possibly also of the forced expiration technique (FET)[1]. There exists no study in which the effect of positive expiratory pressure in vivo on clearance in separate regions of the lungs has been evaluated.

The aim of this study was to assess by means of an objective radio-aerosol technique the effect of PEP on regional lung clearance in patients with chronic bronchitis, as compared with FET, which included postural drainage (PD).

Methods

Patients

Seven patients (6 males, 1 female) with chronic bronchitis according to the MRC criteria[4] took part in the study. Their mean age was 62 (range 48-73) years. The mean FEV_1 was 56 ($SD \pm 21$) % predicted, the mean FVC 75 ($SD \pm 29$) % predicted, and the mean $FEV_1/VC\%$ 64 ($SD \pm 22$)% predicted. The mean sputum production was 32 (range 16-58) grams/day.

Study design

In order to standardize the treatment as much as possible only two experienced physiotherapists participated in the study. PEP included positive expiratory pressure mask (Astra-Meditec, The Netherlands) breathing for two minutes at a level of 10-15 cm H_20 sitting with the elbows resting on a table, followed by a few cycles of abdominal breathing after which the patient performed a few huffs (maximal forced expirations from mid-lung volume). Mobilized secretions reaching the central airways were cleared by coughing. This procedure was performed five times resulting in a total duration of about twenty minutes.

FET was applied according to standard procedures[5] and was combined with PD. This consisted of six positions of which four lying on a tilted bed (15° head down) and two in the sitting position (leaning 45° forward and 30° backward respectively). In every position the patient was instructed to start with diaphragmatic breathing. When the patients had relaxed sufficiently this was followed by thoracic expansion exercises and again diaphragmatic breathing. Then followed 2 huffs with chest compression alternated with relaxed diaphragmatic breathing. If necessary, the patient did cough. The duration of a FET-session was about 30 minutes.

Both PEP and FET with PD were performed without aid. During the control measurement the patient had no physiotherapy and coughed only spontaneously. In each patient the three measurements (PEP, FET with PD and control) were performed in a randomized order on separate days with at least two days in between.

Medication was continued unaltered during the study. The clinical condition of the patient had to be stable for at least six weeks prior to and during the study period.

The patients were informed about the design and the aims of the study. Written informed consent was obtained. The study was approved by the Medical Ethics Committee of the hospital.

Test parameters

The effect of either treatment was assessed by measuring the clearance of an inhaled radio-aerosol. The aerosol consisted of monodisperse 5 μm ^{99m}Tc labelled polystyrene particles[6] and was inhaled under standardized conditions.

Regional lung clearance was calculated by means of gamma camera imaging as described by Agnew et al.[7] with the exception of the correction for alveolar deposition. A posterior 40,000 count image was recorded directly before and after each therapy session. Each subject also had a 200,000 count posterior ventilation study using radioactive krypton (^{81m}Kr). The gamma camera images were recorded in 64x64 format with a MDS computer system (MDS-A[2], Medtronic Medical Data Systems, Ann Arbor, Michigan, USA). By means of the contours of the ^{81m}Kr image a 5x8 matrix was fitted on each lung. Thereby the lungs were divided into inner, intermediate and peripheral zones (see figure 1). Regional clearance after physiotherapy, and in the control run after a similar time lapse, was expressed as percentage of the count rate in a particular zone before the treatment plus the cumulative loss of count rate from more peripheral zone(s)[7].

To estimate the deposition pattern of the radio-aerosol both 24 h retention and penetration index were calculated. 24 h retention of the radio-aerosol was determined as described by Pavia et al.[8]. For this the radio-activity in the thorax was measured by means of two horizontally opposed scintillation detectors, one was positioned in front and the other behind the seated patient. Measurements were made directly after and at 24 hours after inhalation of the radio-aerosol. Furthermore, using the gamma

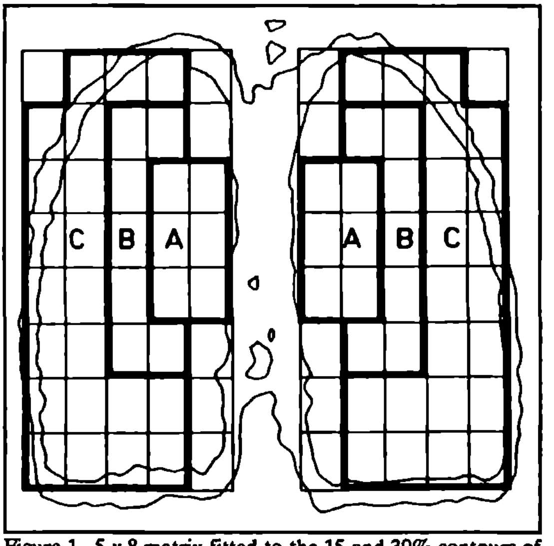

Figure 1. 5 x 8 matrix fitted to the 15 and 30% contours of the ^{81m}Krypton ventilation image. A: inner zone; B: intermediate zone; C: peripheral zone.

camera data, the penetration index (PI) of the radio-aerosol was calculated as described by Agnew et al.[9].

The Wilcoxon test for paired data was used to evaluate the significance of any differences observed.

Results

No significant difference was found between the values for 24 h retention in the three measurements. The mean values were 31 (SD±20)% after PEP, 28 (SD±14)% after FET with PD and 34 (SD±19)% in the control run. Neither was there a significant difference between the PI values. The mean values were 0.51 (SD±0.24) for PEP, 0.46 (SD±0.23) for FET with PD and 0.55 (SD ± 0.23) in the control run. The results of the calculated regional lung clearance are shown in figure 2. The mean clearance in all three lung zones was largest after FET with PD as compared with PEP and control. Statistical significance ($P \leq 0.02$) was reached only for clearance in the inner region after FET with PD as compared with both PEP and control.

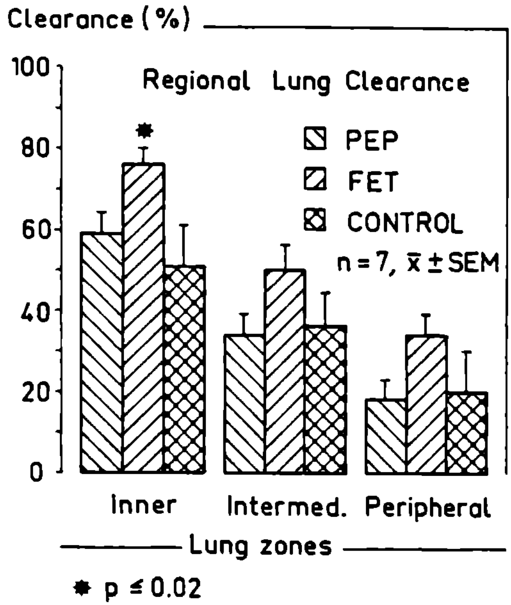

Figure 2. Mean clearance from the peripheral, intermediate and inner zone after PEP, FET with PD and control

Discussion

The purpose of this cross-over study was to assess the effect of PEP-mask physiotherapy on regional lung clearance particularly in the peripheral airways as compared with FET. There exists no such study until now.

In this type of study comparison of the individual results is allowed only if there is little variation in aerosol deposition in each patient. Therefore a monodisperse aerosol was used. The inhalation procedure was standardized. The values of 24 h retention, which is considered an estimate of aerosol deposition in the non-ciliated regions in the lungs, did show no consistent differences between the three runs (PEP, FET with PD and control). Nor did the results of the calculated PI, which is another estimate of aerosol deposition.

In the calculation of the regional lung clearance no correction has been made for alveolar deposition as described by Agnew et al.[7]. As a consequence thereof regional clearance is probably underestimated. This holds particularly true for the peripheral region because deposition in alveoli compared with deposition in conducting airways is largest in this region. This correction has not been made because gamma camera images at 6 hours after inhalation of the radio-aerosol have not been recorded. These are necessary to calculate the estimate of alveolar deposition. To our experience the amount of radioactivity present in the lungs at 6 hours after inhalation is so little, that gamma camera images show rather poor statistics. Furthermore this was a cross-over study, so there was no strong need for such a correction. As shown in figure 2, the mean clearance in every lung region (inner, intermediate and peripheral) is largest after FET with PD. Significance is reached only in the inner region. In every single patient clearance in the inner region was largest after FET with PD. After PEP there is no significant effect at all. These results are in agreement with those reported by Hofmeyr et al.[10]. The effect of PEP and FET with PD on tracheo-bronchial clearance as we have reported earlier do support the findings in the present study[11]. Both PEP and FET with PD in this study included huffing interspersed with diaphragmatic breathing. Because PEP is ineffective, as shown in this study, probably the most effective components of FET with PD are postural drainage and/or the thoracic expansion exercises.

Postural drainage alone has been shown to be effective in mobilizing secretions[12,13]. The additional effect of expansion exercises remains to be elucidated. It is thought that these exercises improve ventilation in atelectatic parts of the lung (5). They are considered an essential part of the FET protocol. Further studies are to be done. In conclusion, the results of this study indicate that PEP has no effect on regional lung clearance. In contrast FET combined with postural drainage appeared to have a significant effect on clearance in central airways.

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Chapter V

No effect of oral high frequency oscillation combined with forced expiration manoeuvres on tracheobronchial clearance in chronic bronchitics

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KEY WORDS: high-frequency, oscillation, vibration, tracheobronchial clearance, physiotherapy, forced expiration technique

ABSTRACT

This study compared the effect of oral high frequency oscillation (OHFO) with the effect of the forced expiration technique (FET) on tracheobronchial clearance. Eight patients with chronic bronchitis were investigated (mean age 60 ±10 yrs, mean FEV_1 68 ±27% predicted, mean sputumproduction 33 ±9 g/day). OHFO was applied at the respiratory system resonant frequency of each patient (range 9.2-25 Hz) and combined with huffing. FET included breathing exercises, huffing and postural drainage. Duration of both OHFO and FET was 30 minutes. Tracheobronchial clearance was measured by means of a radio-aerosol thechique. At 60 minutes after start of the treatment mean tracheobronchial retention was 70 ±26% after OHFO, 54 ±26% after FET and 76 ±18% in the control run, which included huffing only. OHFO was not significantly different from control. FET was significantly different ($p < 0.02$) from both OHFO and control.

It is concluded that OHFO has no effect on tracheobronchial clearance in chronic bronchitics.

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Introduction

In 1985 oral high frequency oscillation (OHFO) has been reported to increase mucociliary clearance in normal man.[1] Since then it has been applied experimentally as a means of improving clearance of excessive bronchial secretion. Reports of its effectiveness in this respect show conflicting results varying from a significant increase in tracheobronchial clearance after OHFO combined with postural drainage and forced expiration[2] to no direct beneficial effect on tracheobronchial clearance but only improvement in mucus transport through stimulation of the coughing reflex.[3] The mechanism through which OHFO exerts its effect – if any – remains unclear. It has been suggested that OHFO changes the characteristics and/or production of mucus or does interact with ciliary beating. Whatever the mechanism might be it seems obvious that the effect of OHFO must be maximal when applied at respiratory system resonant frequency.[1] It is possible to determine respiratory system resonant frequency by means of the forced oscillations technique (FOT).[4]

In this study in each patient resonant frequency was measured by means of the FOT in order to apply OHFO at his or her specific resonant frequency. The aim of the study was to evaluate the effect of OHFO at respiratory system resonant frequency when combined with forced expiration manoeuvres (huffing) on tracheobronchial clearance. This was compared with the effect of huffing alone and huffing in combination with breathing exercises and postural drainage (FET).

Methods

Patients

Eight patients with chronic bronchitis as defined by the Medical Research Council[5] took part in the study. Their mean age was 60 yrs (range 44-76 yrs). The mean forced expiratory volume in one second (FEV_1) was 68 (SD ± 27)% predicted. The mean forced vital capacity (FVC) was 92 (SD ± 20)% predicted. The mean FEV_1/FVC was 67 (SD ± 19)% predicted. The mean sputum production was 33 (range 22-47) g wet weight per day.

Study design

On three separate days with at least two days in between the effect of the following three treatments was evaluated: (1) oral high frequency oscillation (OHFO); (2) huffing combined with breathing exercises and postural drainage (FET); (3) huffing alone (control). The sequence was determined in a randomized cross-over fashion.

OHFO consisted of oscillations superimposed on tidal breathing during one period of 30 minutes. Every 5 minutes OHFO was interrupted to perform a few huffs (maximal forced expirations from mid-lung volume). If necessary the patients coughed. OHFO was applied at respiratory system resonant frequency. This frequency had been determined on the same day prior to radio-aerosol inhalation by means of the FOT[4] using the Oscillaire (Jones, USA). Resonant frequencies ranged from 9.2-25 H_z. Sinewave oscillations were produced by a 20 cm bass loudspeaker (Philips AD 80602 W8) connected to a waveform generator (Exar, XR-8038). Stroke volume of the oscillations ranged from 60-250 ml. Oscillations were delivered to the subject through a 50 cm semirigid tube (internal diameter 2.5 cm) attached to a mouthpiece. A side arm in the tube was connected to a humidifier (see figure 1). The patients were sitting with the elbows resting on a table. No postural drainage was performed.

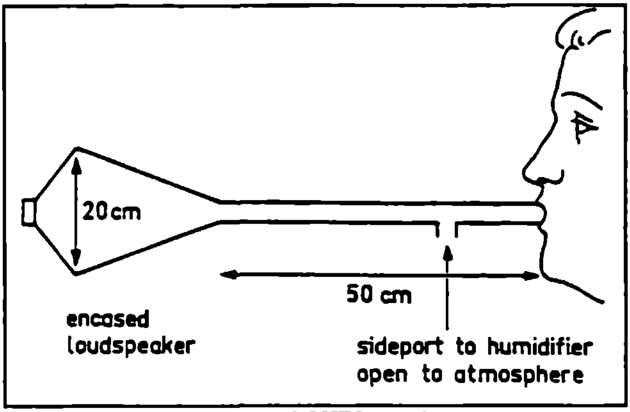

Figure 1. Schematic diagram of OHFO – delivery system.

FET was applied according to standard procedures.[6,7] Only two experienced physiotherapists participated in the study in order to standardize the treatment as much as possible. FET included postural drainage consisting of six positions, four lying on a tilted bed (15° head down) and two seated (leaning 45° forward and 30° backwards respectively). In every position the patient was instructed to start with diaphragmatic breathing. When the patient had relaxed sufficiently this was followed by thoracic expansion exercises and again diaphragmatic breathing. Then followed two huffs (maximal forced expirations from mid-lung volume) with chest compression alternated with relaxed diaphragmatic breathing. If necessary the patient coughed. FET was performed without aid. Prior to the start of the study the patient had been instructed by the physiotherapist to perform the FET. The duration of the FET session was thirty minutes. During FET the patient was breathing ambient air.

The control treatment consisted of breathing humidified air for 30 minutes through the mouthpiece of the switched off OHFO-generator, while sitting with the elbows resting on a table. No postural drainage was performed. Every 5 minutes this was interrupted to perform a few huffs. If necessary the patient coughed.

Any medication was continued unaltered. The clinical condition of the patients as judged by lung function tests had to be stable for at least six weeks prior to and during the study period. The patients were informed about the design and the aim of the study. Written informed consent was obtained. The study was approved by the Medical Ethics Committee of the University Hospital.

Test parameters

Tracheobronchial clearance was measured using a radio-aerosol technique.[8] A monodisperse 5 μm ^{99m}Tc-labelled polystyrene particle aerosol was inhaled under standardized conditions. The radioactivity in the thorax was measured by means of two horizontally opposed scintillation detectors. One detector was placed in front of the seated subject and centred midway the sternum, and the other behind the subject and centred at the spinal column. Measurements were started directly after inhalation of the radio-aerosol and repeated at regular intervals i.e. approximately every 20 minutes up to 6 hours after inhalation and once more at 24 h after inhalation. As described by Pavia et. al.[9] the sum of the radioactivity count rates of the two detectors was corrected for background activity, isotope decay and 24 h retention. The latter is considered to be an estimate of the aerosol deposition in the non-ciliated regions of the lung. The corrected count rate was expressed as a percentage of the count rate assessed immediately before the start of the treatment (OHFO, FET or control). These percentages were plotted against time after start of the treatment thus resulting in tracheobronchial retention curves. The area under the retention curves of each individual measurement was calculated using non-fitted data.

The area under the retention curve up to 2.5 hours after start of the treatment (AUC-2.5) was used to evaluate the effect of the treatment.[10]

Lung function was measured just before inhalation of the radio-aerosol and at about 1 hour after physiotherapy, including a flow volume curve and sGaw by means of a body plethysmograph (Jaeger Bodyscreen II). Sputum was collected during the therapy, and during the rest of the day. Sputum wet weight was measured. In addition sputum was dried for 72 hrs at 50°C to determine sputum dry weight. The Wilcoxon test for paired data was used to evaluate the significance of any differences observed.

Results

No significant difference between the values of 24 h retention after OHFO, FET or Control treatment was found. The mean 24 h retention which stands for alveolar deposition was 34 (SD ± 18)%, 36 (SD ± 21)% and 35 (SD ± 18)%. The mean curves of tracheobronchial retention after OHFO, FET and control are presented in figure 2. At 40 and 60 minutes there is a significant difference between FET and both OHFO and control ($p<0.02$). At 80 minutes there is a significant difference between

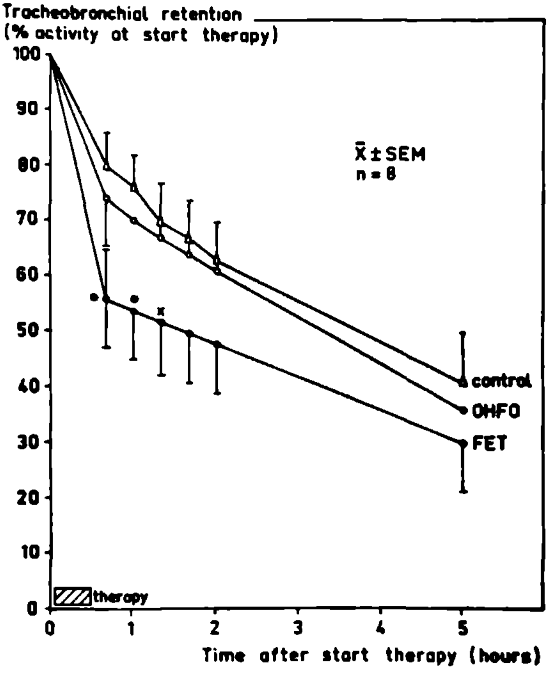

Figure 2. Mean tracheobronchial retention curves during and after control, OHFO and FET.
* $p<0.02$ FET vs OHFO and control
x $p<0.05$ FET vs OHFO.

FET and OHFO only ($p<0.05$). In table 1 the results of the area under the curve up to 2.5 hrs after the start of therapy (AUC-2.5) are presented. In all patients the AUC-2.5 was smallest after FET as compared with both OHFO and control ($p<0.02$). There appeared to be no significant difference in AUC-2.5 between OHFO and control. In table 2 the results of the measurement of lung function are presented. There appeared to be no consistent effect of any of the three therapies. The results of the measurement of the collected sputum are presented in table 3. Sputum production during FET was significantly ($p<0.02$) larger than during both OHFO and control.

Table 1. Area under the curve 0-2.5 hours after start of therapy (AUC-2.5) (%hours) of each patient for FET, OHFO and control respectively.

Patient No.	FET	OHFO	control
1	207	222	228
2	66	103	184
3	129	140	173
4	162	185	189
5	193	236	198
6	109	229	194
7	79	101	103
8	209	213	220
Mean	144	179	186
SD	58	56	38

Table 2. Lung function data before and after therapy (n = 8, mean ± SD).

	before	after	before	after	before	after
	FET		OHFO		control	
FEV_1 (1)	2.3±1.0	2.2±1.0	2.2±1.0	2.1±1.0	2.3±1.0	2.2±1.0
FVC (1)	4.0±1.1	3.8±1.1	3.9±1.0	3.6±1.0	3.9±1.1	3.8±1.1
MEF_{50} (1/sec)	1.5±1.0	1.5±1.1	1.6±1.2	1.5±1.2	1.5±1.0	1.6±1.1
sGaw (1/sec.kPa)	0.77±0.36	0.76±0.44	0.69±0.25	0.72±0.39	0.85±0.38	0.76±0.43

Table 3. Sputum production (n = 8, mean ± SD).

	FET	OHFO	CONTROL
During therapy	201 ± 145*	43 ± 62	29 ± 42 mg dry weight
24 h production	36 ± 12	31 ± 10	32 ± 9 g wet weight

* $p<0.02$ as compared with OHFO and Control.

Discussion

The aim of this study was to evaluate the effect of OHFO on tracheobronchial clearance in patients with chronic bronchitis and abundant sputum production. In the study by George et al.[1] resonant frequency was determined by the subjects themselves on the basis of their sensation of shaking within the chest. This frequency ranged from 8-12 H_z. In our study OHFO was applied at a predetermined frequency identical to respiratory system resonant frequency as measured by means of FOT. This ranged from 9.2 to 25 H_z. Apart from the frequency of the oscillations, the volume thereof could be varied individually as well. The latter was adjusted in such a manner that it was possible to feel the oscillations by hand over the thorax of the patients or to hear them by stethoscope over the lungs without the oscillations causing too much discomfort to the patients. Apart from the oscillations OHFO in this study consisted of forced expiration manoeuvres at 5-minute intervals. George et al.[1] suggest that the mechanism by which OHFO is effective in promoting mucus clearance is by altering the visco-elastic properties of airway mucus. King[11] has reported that high frequency oscillation reduces the apparent viscosity of sputum in vitro. In the same study has been demonstrated that a decrease in mechanical impedance (i.e. the vectorial sum of elasticity and viscosity) of mucus appears to have a positive effect on clearance induced by in vitro simulated cough. Assuming that these results are also valid for forced expirations it seems logical to combine OHFO with forced expiration manoeuvres as performed in our study. However, the results reported by King have been questioned by Hachenberg et al.[12] The latter reported a slight but significant increase in viscosity under high-frequency vibration. There appeared to be no significant difference in any of the parameters between OHFO and a control measurement, which consisted only of forced expiration manoeuvres at 5-minute intervals for 30 minutes. FET including forced expiration manoeuvres, breathing exercises and postural drainage appeared to be significantly more effective than both OHFO and control (see figure 2 and table 1 and 3). Probably the most essential difference between FET and OHFO is postural drainage. In this respect it is important to realize that George et al. reported a significant enhancement of tracheobronchial clearance in cystic fibrosis patients only when OHFO was combined with physiotherapy including postural drainage.[2] Although in our study essentially different equipment to generate oscillations has been used, our results of OHFO are in agreement with those reported by Ravez et al.[3] The fact that George et al.[1] found an enhancement in tracheobronchial clearance caused by OHFO in normal subjects might suggest that OHFO can be beneficial only in the presence of normally effective mucociliary clearance and not in the presence of excessive bronchial secretions and /or failing mucociliary transport. The suggestion by the same authors that OHFO exerts its effect mainly in distal airways is not supported by the results in our study (see fig. 2). The difference between the study of George et al.[1] and our study with regard to the time during which OHFO has been applied could provide an explanation for the contradictory results. Several authors have described the effect of nonsymmetrical flow on mucus transport in vitro.[13-15] This effect of oscillatory flow has been seen in an animal study in which dogs were ventilated by means of chest wall oscillation.[16] The oscillations delivered to the subjects in our study were symmetrical. Furthermore, these oscillations were superimposed on spontaneous tidal breathing. Therefore the described mechanism[13-15] by which nonsymmetrical flow causes mucus transport does not seem to be applicable to our results.

On the basis of the results of our study it must be concluded that OHFO as applied in this study in combination with forced expiration manoeuvres does not improve tracheobronchial clearance of excessive bronchial secretions in patients with chronic bronchitis.

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Chapter VI

No difference in effectiveness of a mucolytic, a hypertonic or an isotonic saline aerosol when combined with forced expiration manoeuvres

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SUMMARY

The purpose of this study was to evaluate the effect of an inhaled mucolytic in combination with the forced expiration technique (FET) on tracheobronchial clearance. Eight patients with chronic bronchitis and abundant sputum production inhaled on three separate days in a double blind randomized cross-over fashion one of the following nebulized solutions:
(A) mercaptoethane sulphonate (Mistabron^R), (B) hypertonic saline, (C) isotonic saline. Clearance was measured using a radio-aerosol technique.

There were no significant differences in tracheobronchial retention between aerosol A, B and C directly after inhalation and prior to the start of physiotherapy. After completion of FET there appeared to be no difference in tracheobronchial retention between the three treatments.

It is concluded that there is no significant difference in effect of inhalation of Mistabron^R, hypertonic saline or isotonic saline when combined with FET including postural drainage in chronic bronchitics.

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Introduction

Treatment with mucolytics is common practice in patients with troublesome expectoration. However, objective evidence for the effectiveness of inhaled mucolytic drugs in mobilizing excessive bronchial secretions is rather scarce.[1,2] The supposed enhancement of clearance by mucolytics is thought to be due to either reduction of the viscosity by breaking down disulphide bonds[3] or to reduction of the consistency by a direct osmotic effect.[1] This remains to be elucidated.

The combination of inhaled mucolytics with chest physical therapy seems logical in order to achieve maximal clearance of excessive secretions. No study so far has evaluated the effect of this combination on tracheobronchial clearance using an objective in vivo radio-aerosol technique. The aim of this study was to compare the effect of an inhaled mucolytic (Sodium mercaptoethane sulphonate) with that of a hypertonic and an isotonic saline aerosol, all three combined with a forced expiration technique (FET) session.

Patients

Eight patients with chronic bronchitis as defined by the Medical Research Council criteria[4] took part in the study. Their mean age was 65 yrs. (range 52-73 yrs). The mean forced expiratory volume in one second (FEV_1) was 86 (SD ± 25)% predicted. The mean FEV_1/VCin % was 84 (SD ± 23)% predicted. The mean sputum production was 39 g (range 18-83 g) per day.

Study design

On three separate days – with at least two days in between – the treatment consisted of the inhalation of an aerosol followed by a FET session. On each occasion in a double blind randomized order one of three different aerosol solutions (A, B and C) was nebulized by means of a jet nebulizer (Pari Inhalierboy^R) and inhaled through a mouthpiece. Sterk et al have studied the output characteristics of several nebulizers.[5] The volume median aerodynamic diameter ($VMAD_d$) of the primary droplets produced by the Pari Inhalierboy^R appeared to be 3.5 μm.

In table 1 the composition and osmolality of these solutions is listed. The sequence of the applied solutions was determined in a double blind randomized crossover mode.

The inhalation of the aerosol took 20-25 minutes and was followed by a FET session according to standard procedures.[6] This included postural drainage consisting of six positions, four lying on a tilted bed (15° head down) and two seated (leaning 45° forward and 30° backwards respectively). In every position the patient was instructed to start with diaphragmatic breathing. When the patient had relaxed sufficiently this was followed by thoracic expansion exercises and again diaphragmatic breathing. Then followed two huffs (maximal forced expirations from mid-lung volume) with

Table 1. Composition and osmolality of the aerosol solutions.

Solution	Composition		Osmolality (mOsm/1)
A.	Sodium mercaptoethane sulphonate		
	(Mistabron[R])	400 mg	1125
	terbutaline sulphate	0.5 mg	
	in sodium chloride 0.54%	5 ml	
B.	terbutaline sulphate	0.5 mg	1090
	in sodium chloride 3.38%	5 ml	
C.	terbutaline sulphate	0.5 mg	
	in sodium chloride 0.9%	5 ml	333

chest compression alternated with relaxed diaphragmatic breathing. If necessary the patient coughed. FET was performed without aid. Prior to the start of the study the patient had been instructed by a physiotherapist to perform the FET. The duration of the FET session was thirty minutes. Only two experienced physiotherapists participated in order to standardize the treatment as much as possible. Medication was continued unaltered during the study, but mucolytic drugs were not allowed. The clinical condition of the patients had to be stable for at least six weeks prior to and during the study period. The patients were informed about the design and the aims of the study. Written informed consent was obtained. The study was approved by the Medical Ethics Committee of the University Hospital.

Test parameters

Tracheobronchial clearance was measured using a radio-aerosol technique.[7] A monodisperse 5 μm ^{99m}Tc-labelled polystyrene particle aerosol was inhaled under standardized conditions. The radioactivity in the thorax was measured by means of two horizontally opposed scintillation detectors. One detector was placed in front of the seated subject and centred at the sternum, and the other behind the subject and centred at the spinal column. Measurements were started directly after inhalation of the radio-aerosol and repeated directly prior to and after inhalation of aerosol A, B or C, and directly after the FET session. Up to several hours after the start of the inhalation of the aerosol measurements were repeated at 30-minute intervals and once more at 24 h after radio-aerosol inhalation. As described by Pavia et.al.[8] the sum of the radio-activity count rates of the two detectors was corrected for background activity, isotope decay and 24 h retention. The latter is considered to be an estimate of the aerosol deposition in the non-ciliated regions of the lung. The corrected count rate was expressed as a percentage of the count rate assessed immediately before the start of the inhalation of aerosol A, B or C. These percentages were plotted against time after the start of inhalation of aerosol A, B or C, thus resulting in tracheobronchial retention curves.

Lung function was measured just before inhalation of the radio-aerosol and at about 1 hour after physiotherapy, including a flow volume curve and sGaw by means of a body plethysmograph (Jaeger Bodyscreen II). Sputum was collected during the FET session, and during the rest of the day. Sputum wet weight was measured. In addition sputum was dried for 72 h at 50°C to determine sputum dry weight. The Wilcoxon test for paired data was used to evaluate the significance of any differences observed.

Results

No significant differences between the values of 24 h retention of the radio-aerosol after the mucolytic, hypertonic or isotonic saline aerosol were found. The mean 24 h retention which represents alveolar deposition was 43 (SD ± 24)%, 44 (SD ± 19)% and 44 (SD ± 16)% respectively.

The mean curves of tracheobronchial retention during and after the mucolytic, the hypertonic and isotonic aerosol are presented in the figure. With respect to the tracheobronchial retention at 30 min. and 60 min. after the start of the inhalation of the aerosol i.e. after completion of the inhalation (30 min.) and after the FET session (60 min.) there appeared to be no significant difference in tracheobronchial retention between the three treatments. At 2 h after the start of inhalation of the mucolytic, the hypertonic and the isotonic aerosol the tracheobronchial retention appeared to be 25 (SD ± 9)%, 19 (SD ± 11)% and 24 (SD ± 17)% respectively, being not significantly different.

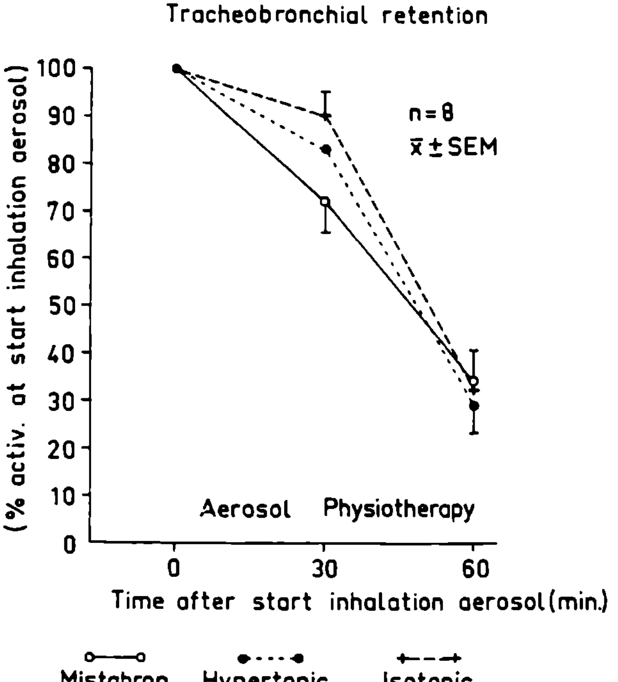

Figure 1. Mean tracheobronchial retention curves during and after the mucolytic (0–0), the hypertonic (●–●) and the isotonic (+–+) aerosol.

The results of the lung function measurement before and after treatment are listed in table 2. There appeared to be no significant difference between the effects of the three treatments. Statistical significance was reached only for the results of the measurement of FEV_1 and sGaw after inhalation of hypertonic saline as compared with those before inhalation. The results of the measurement of sputum wet and dry weight are listed in table 3. The differences between the three treatments are not statistically significant.

Table 2. Lung function data before and after aerosol inhalation combined with FET (n = 8).

	MIST. before	MIST. after	HYPERT. before	HYPERT. after	ISOTON. before	ISOTON. after
Mean FEV_1 (l)	2.08	2.19	2.09	2.30*	2.07	2.15
SD	0.8	1.0	0.7	0.7	0.7	0.8
Mean FVC (l)	3.2	3.3	3.2	3.4	3.2	3.1
SD	0.8	1.0	07.	0.7	0.8	0.8
Means sG_{aw}	0.789	0.876	0.809	0.991**	0.829	1.08
SD	0.26	0.32	0.37	0.39	0.33	0.53
$(kPa.sec)^{-1}$						

* $p < 0.05$ as compared with the FEV_1 before treatment
** $p < 0.02$ as compared with the sG_{aw} before the treatment.

Table 3. Data on sputum production (mean ± SD), (n = 8).

	Mistabron	Hypertonic saline	Isotonic saline
sputumproduction during FET			
wet weight (g)	7.8 ± 6.5	6.9 ± 2.5	6.1 ± 3.5
dry weight (mg)	120 ± 120	132 ± 98	125 ± 102
24 h sputum production			
wet weight (g)	37.7 ± 18	36.5 ± 10	43 ± 24

Discussion

In the present study no statistically significant differences between the effect on tracheobronchial clearance of treatments consisting of inhalation of three different aerosols (a mucolytic drug, a hypertonic and an isotonic saline solution) followed by FET could be found.

Clarke et al.[1] reported an enhancement in tracheobronchial clearance in chronic bronchitics after inhalation of Mistabron^R, however the difference was not statistically significant. In the same study the inhalation of hypertonic saline (7.1%) appeared to be more effective than Mistabron^R though. They suggested that the enhanced clearance after the hypertonic saline aerosol was due to a local osmotic effect resulting in water being drawn into the airway lumen. In this context it must be pointed out that in our study solution B consisted of a much weaker saline solution i.e. 3.38% (see also table 1). A possible osmotic effect therefore would have been less than in the study reported by Clarke et al.[1] In another study[2] an improvement in pulmonary function was found in patients with cystic fibrosis after an eight-week course of intermittent Mistabron^R inhalation. This effect was not seen after inhalation of iso-osmolar hypertonic saline (7%). There were no changes in cough frequency, sputum volume, sputum bacteriology or symptom scores. In our study in patients with chronic bronchitis no significant differences in tracheobronchial retention were found after inhalation of Mistabron^R, hypertonic and isotonic saline. All three aerosol solutions contained 0.5 mg terbutaline. This drug was added in order to prevent bronchoconstriction.[9] Subcutaneously administered ß-mimetic drugs stimulate mucociliary clearance.[10,11] Reports on the effect of inhaled ß-mimetic drugs on tracheobronchial clearance show conflicting results. Pavia et al.[12] utilizing exactly the same technique for measuring clearance as used in our department, failed to demonstrate an effect of inhaled terbutaline on mucociliary clearance. Foster et al.[13] and recently Weich et al.[14] – using a different technique – described the enhancement of clearance after inhalation of isoproterenol and fenoterol respectively. In our study solution C containing terbutaline and sodium chloride 0,9% was meant to serve as a control measurement in order to evaluate the effect of the hypertonic solutions A and B (see table 1). The differences in tracheobronchial retention after inhalation of Mistabron, hypertonic saline and isotonic saline before physiotherapy was started, appeared to be not significant. After FET was completed retention was practically identical, suggesting that any difference in effectiveness of any of the three aerosols had been annihilated by a physiotherapy session, including postural drainage.

The forced expiration technique combined with postural drainage has been shown to be an effective means of accelerating clearance of excess bronchial secretion.[15,16] Means of improving this effect have been studied by Sutton et al.[17] They reported that the use of nebulized terbutaline immediately before FET enhanced clearance significantly more than FET alone. The amount of terbutaline nebulized in their study was 5 mg as opposed to 0.5 mg in our study .

After the inhalation of all three aerosols followed by FET lung function variables showed an improvement. After inhalation of hypertonic saline followed by FET there was a statistically significant improvement in FEV_1 and sGaw. In our former study[16] we did not find an improvement in lung function at all. Therefore the improvement in lung function in the present study is probably due to the inhalation of terbutaline.

The results of the measurement of sputum production are in agreement with those of the measurement of radioaerosol clearance, i.e. no significant differences were found between the three treatments. Inhalation of the hypertonic solutions A and B did not result in a significantly larger amount of sputum. Therefore there are no indications for a possible osmotic effect caused by the hypertonic aerosols. It is concluded that there is no significant difference in effect on tracheobronchial clearance of inhalation of Mistabron^R, hypertonic saline or isotonic saline when combined with a FET session including postural drainage.

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Chapter VII

Patients with dextrocardia do have tracheobronchial clearance other than by coughing alone

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Key words: tracheobronchial clearance, cough clearance, situs inversus, dextrocardia.

ABSTRACT

In 6 patients with dextrocardia (DC) tracheobronchial clearance was measured by means of a radio-aerosol technique (5 micron ^{99m}Tc labelled polystyrene particles). The retention curves were corrected for expectorated sputum in order to rule out as much as possible the effect of so-called cough clearance. In 2 patients clearance after sputum correction was practically absent, i.e. 6 hours after inhalation there was 82 and 83% tracheobronchial retention. In the remaining 4 patients this was 56, 55, 46 and 42%. The mean tracheobronchial clearance of all DC patients was significantly slower than the mean clearance of 10 healthy non-smoking subjects, but not significantly different from that of 6 patients with chronic bronchitis, who were all current smokers. It is concluded, that in some patients with dextrocardia, Kartagener's patients included, there exists a decreased, but effective clearance, even after correction for cough clearance.

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Introduction

In 1933 Kartagener described four patients presenting with the combination of situs inversus, sinusitis and bronchiectasis.[1] This triad is referred to as Kartagener's syndrome (KS). Originally the bronchiectases in these patients were thought to be congenital. Today it is a widely accepted view, that they are caused by recurrent purulent respiratory tract infections. KS appears to be associated to a high degree with infertility, although there have been several reports of KS patients with descendants.[2-5] The first reports of sperm tail immotility focused attention on ciliary abnormalities as a possible cause of the recurrent respiratory tract infections.[6] Since 1976 several specific abnormalities in the ciliary ultrastructure associated with ciliary immotility or dyskinesia have been reported in KS patients.[7-13] Also KS patients with normal cilia have been described.[14,15] In conclusion there appears to exist a whole spectrum of congenital ciliary abnormalities of both structure and function. Mucociliary clearance is thought to be an important host defence mechanism of the respiratory tract. Absence of mucociliary clearance is considered to be a hallmark of the primary ciliary dyskinesia syndrome.[16] It is therefore difficult to understand, why patients with the primary ciliary dyskinesia syndrome, KS patients included, appear to have a relative good life expectancy. It has been suggested by Afzelius, that ciliary malfunction in the embryonic phase causes situs inversus in half the patients in a randomized fashion.[17] This would imply that every patient with situs inversus, including dextrocardia, must have congenital ciliary malfunction.

The aim of this study was to establish the presence or absence of tracheobronchial clearance other than caused by cough in patients with dextrocardia. For this the radio-aerosol technique described by Thomson and Short[18] was used. The results of the DC patients were compared with those of healthy non-smoking subjects and those of patients with chronic bronchitis (CB).

Patients

Six patients with dextrocardia were investigated. Dextrocardia is defined as lateral transposition of the viscera of the thorax. Individual lung function data are listed in table 1.

Table 1. Individual lung function data of the DC patients.

Patient No.	FVC (litre)	(%pred.)	FEV_1 (litre)	(%pred.)	FEV_1/FVC (%)	(%pred.)
1.	3.0	(91)	1.6	(60)	53	(80)
2.	4.5	(79)	2.7	(58)	59	(81)
3.	5.5	(101)	4.5	(108)	82	(76)
4.	2.7	(73)	1.8	(67)	68	(74)
5.	5.0	(91)	4.1	(93)	83	(81)
6.	2.6	(68)	1.4	(57)	54	(65)

Only patient no.1 was current smoker, i.e. smoked very rarely. Patient no. 6 was ex-smoker with 49 pack-years. The remaining 4 DC patients were all non-smokers. All patients, except patient no. 6, did have both upper (ENT) and lower respiratory tract symptoms. Individual clinical data of the DC patients are listed in table 2.

Table 2. Individual clinical data of dextrocardia patients.

Patient No/Age/Sex	Sputum culture	Bronchography
1 / 20 / F	Hem. Infl.	ectases left + right side
2 / 17 / M	Hem. Infl./Strept.Pneum.	ectases left lower lobe
3 / 24 / M	Hem. Infl./Strept.Pneum.	ectases left lower + middle lobe
4 / 38 / F	Hem. Infl.	-----
5 / 16 / M	Hem. Infl./Strept.Pneum.	no visualization of middle lobe + lingula
6 / 66 / M	negative	no ectasis

For comparison of tracheobronchial clearance results the data of six patients with chronic bronchitis were used, who were matched for 24h retention. Chronic bronchitis was defined according to the MRC criteria.[19] These patients were all current smokers. The mean number of pack-years was 29.6. The mean age was 58 years, ranging from 37 to 67 years.

Results of the DC patients were also compared with those of 10 healthy non-smoking individuals.

From all patients a signed informed consent was obtained.

Methods

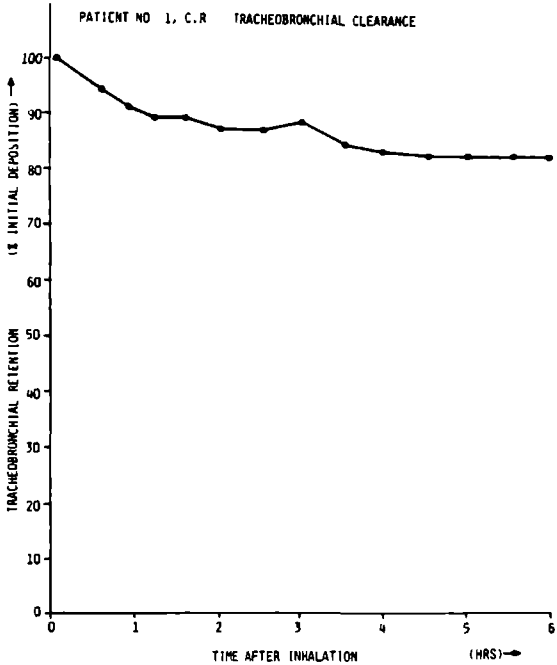
Using a spinning disc generator (R.E. May Spinning Top aerosol generator, Research Engineers Ltd.) a ^{99m}Tc labelled monodisperse 5 micron polystyrene aerosol was produced. This aerosol was inhaled under standardized conditions, i.e. 15 inhalations of 450-500 ml each. The subjects were asked to inhale slowly. There was a 3 seconds breath-holding pause after each inhalation. After inhalation the radioactivity in the thorax was measured at regular intervals for 6 hours by means of two horizontally opposed scintillation detectors consisting of thallium activated sodium-iodide (NaI) crystals. One detector was positioned in front of the seated subject centred midway the sternum and the other behind the subject centred at the spinal column. Interference of activity present in stomach or throat with the measurement of activity present in the lungs was reduced to a minimum by using collimators with an aperture of 9.0 cm diameter at 2.5 cm from the crystal. At 24 hours after inhalation radioactivity was measured once more. This measurement is supposed to be an estimate of radioaerosol deposition in the non-ciliated regions of the lungs, which is also referred to as "alveolar deposition". The sum of the radioactivity count rates of the two detectors was corrected for background activity and isotope decay. The tracheobronchial clearance was then estimated by correcting for 24 h retention. The tracheobronchial retention curve was obtained by plotting tracheobronchial retention (TBRet), expressed as percentage of initial tracheobronchial deposition, against time after inhalation (PIT). During the measurement patients were allowed to cough. They were encouraged to expectorate sputum, when coughing was productive, rather than swallowing it. As described by Pavia et al[20] tracheobronchial retention was corrected for activity measured in expectorated sputum. Coughs were recorded and radioactivity of the sputum samples was measured on a separate NaI crystal (N counts). In order to correct the decrease in intrathoracic activity for the effect of coughing with expectoration of sputum a correction factor was calculated. By means of this correction factor the number of counts measured in the sputum samples was converted to an equivalent number of counts of intrathoracic activity. In this way the radioactivity which was expectorated was added back to the intrathoracic activity. For the calculation of the correction factor first a ^{99m}Tc source was measured (A counts) in the same way as sputum samples were measured. Subsequently this source was positioned in the trachea of a phantom of the thorax (RT-200 phantom, Humanoid Systems). This "intrathoracic" activity was measured (B counts) in the same way as this was done in the subjects. After correction for physical decay this number of counts (B) was divided by the number of counts in the first measurement (A). Therefore in case there had occurred expectoration of any sputum $\frac{B}{A}$ x N counts were added back to the counts of intrathoracic activity.

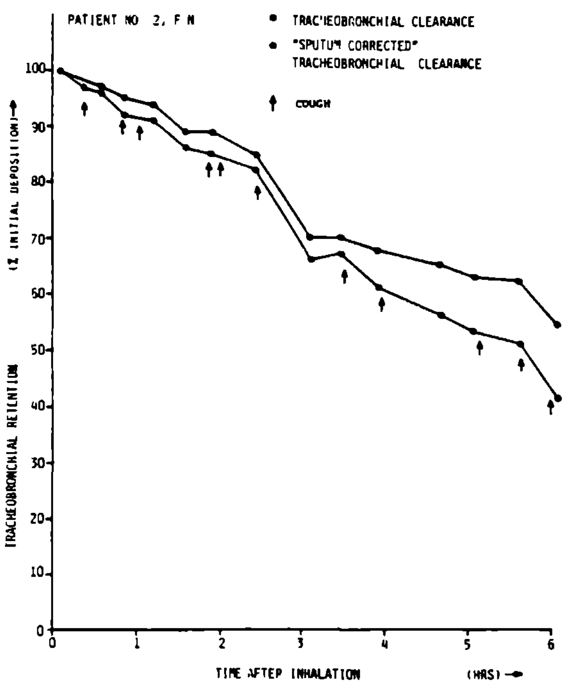
Five patients (nos 1-5) did not take any medication on the day of the measurement. Patient no. 6 had the following medication: beclomethasone dipropionate, theophylline, salbutamol, dipyridamole and clonidine. The mean of the tracheobronchial retention curves was calculated using the interpolated percentages at twenty minute intervals of the individual curves. The two-sample Wilcoxon test was used to evaluate the significance of any observed differences between the different groups of patients.

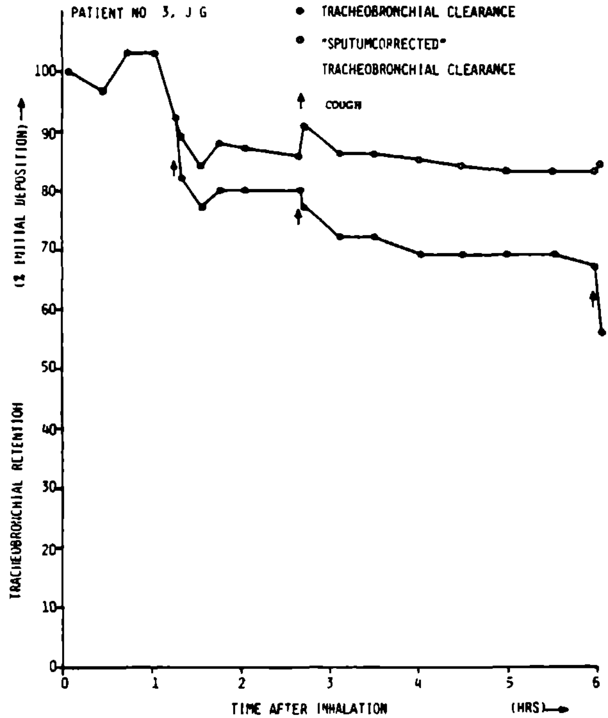
Results

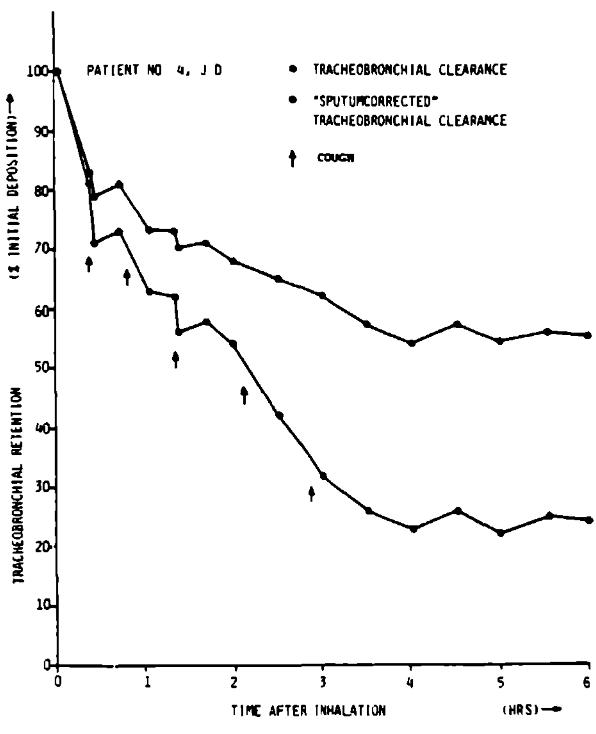
In figures 1-6 individual tracheobronchial retention curves are presented. The arrows in the curves indicate the coughs during the measurement in the individual patients. Patient no. 3 had a cough twice during the measurement. This patient was capable of indicating exactly when he had to cough. Thereby it was possible to measure the intrathoracic activity directly before and after coughing. In table 3 individual data of percentage tracheobronchial retention (TBRet.) at 6 hours after inhalation (6h PIT) and of the percentage 24h retention (24h ret.) are listed. The mean 24h retention of the 6 DC patients was 49% (SD ± 19%). For the 6 CB patients this was 50% (SD ± 17%) and for the healthy non-smoking subjects 52% (SD ± 10%). The mean tracheobronchial retention curves of all DC patients, uncorrected and "sputum corrected", of the chronic bronchitis patients and of the healthy subjects are presented in fig. 7. The mean TBRet. at 6h after inhalation of the 6 DC patients, uncorrected for expectoration, was 48%. "Corrected for sputum" this was 61%. The mean TBRet. at 6h after inhalation of the 6 chronic bronchitis patients and of the 10 healthy subjects was 41 and 18 respectively.

Figure 1-6. Individual tracheobronchial retention curves of dextrocardia patients, uncorrected and corrected for expectorated sputum.






PATIENT NO 3, J G
TRACHEOBRONCHIAL CLEARANCE
"SPUTUMCORRECTED" TRACHEOBRONCHIAL CLEARANCE
COUGH
TRACHEOBRONCHIAL RETENTION (% INITIAL DEPOSITION)
0
10
20
30
40
50
60
70
80
90
100
0
1
2
3
4
5
6
TIME AFTER INHALATION (HRS)


PATIENT NO 4, J D
TRACHEOBRONCHIAL CLEARANCE
"SPUTUMCORRECTED" TRACHEOBRONCHIAL CLEARANCE
COUGH
TRACHEOBRONCHIAL RETENTION (% INITIAL DEPOSITION)
0
10
20
30
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70
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90
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0
1
2
3
4
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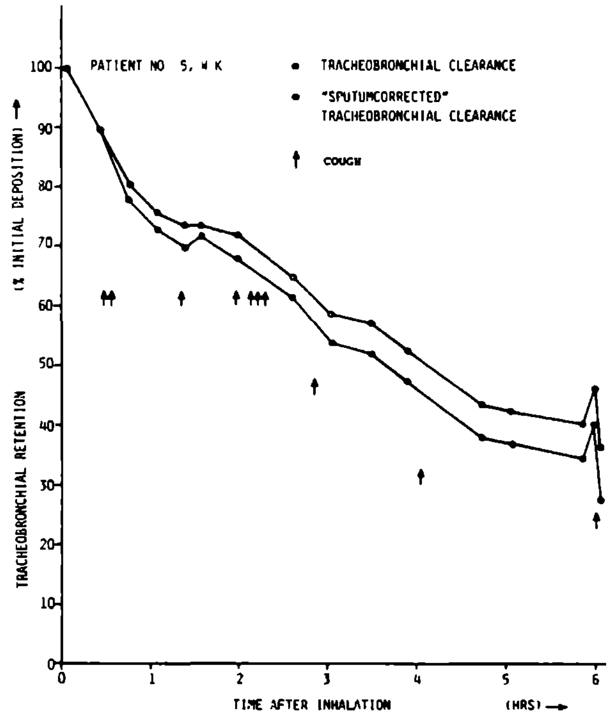
6
TIME AFTER INHALATION (HRS)


PATIENT NO 5, W K
TRACHEOBRONCHIAL CLEARANCE
"SPUTUMCORRECTED" TRACHEOBRONCHIAL CLEARANCE
COUGH
TRACHEOBRONCHIAL RETENTION (% INITIAL DEPOSITION)
TIME AFTER INHALATION (HRS)
0
10
20
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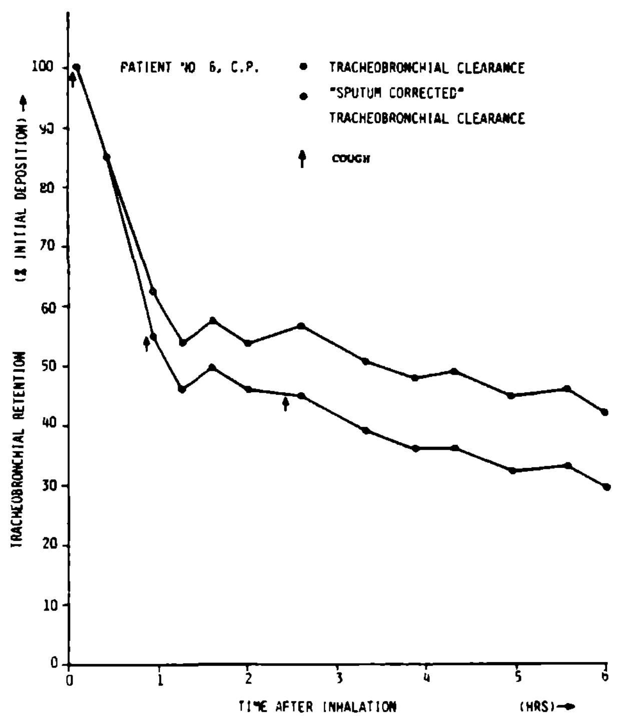
PATIENT NO 6, C.P.
TRACHEOBRONCHIAL CLEARANCE
"SPUTUM CORRECTED" TRACHEOBRONCHIAL CLEARANCE
COUGH
TRACHEOBRONCHIAL RETENTION (% INITIAL DEPOSITION)
TIME AFTER INHALATION (HRS)
0
10
20
30
40
50
60
70
80
90
100
1
2
3
4
5
6

Table 3. Tracheobronchial retention data of the DC patients.

Patient No.	TBRet.(*)at 6h PIT.(**)	TBRet.(*) at 6h PIT.(**) "sputum corrected"	24h ret. (***) (%)
1	82	82	29
2	43	56	22
3	67	83	71
4	24	55	58
5	40	46	59
6	29	42	55

* TBRet. = tracheobronchial retention
** PIT. = post inhalation time
*** 24h ret. = 24 hour retention

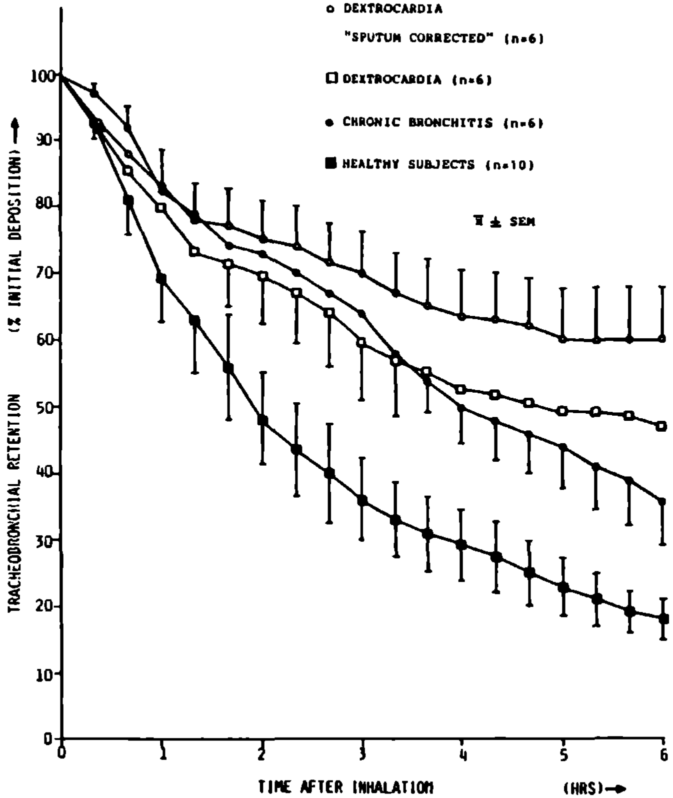

Figure 7. Calculated mean tracheobronchial retention curve ($\bar{x}$ ± SEM) of dextrocardia patients (uncorrected and corrected for expectorated sputum) (n=6), of chronic bronchitis patients (n=6 and healthy individuals (n=10).

There was no statistically significant difference between the mean of the uncorrected tracheobronchial retention curve of the DC patients and the mean curve of the chronic bronchitis patients ($p > 0.1$). Obviously clearance of the DC patients after "correction for expectorated sputum" is slower, but still not significantly different from the CB patients either ($p > 0.1$). The mean of the "sputum corrected" and the uncorrected clearance curves of the DC patients were both significantly different from the mean retention curve of the healthy subjects ($p < 0.05$).

Discussion

In six patients with dextrocardia the tracheobronchial clearance rate was measured. Patients no's 1-5 have a classical Kartagener's syndrome. Patient no. 6 has bronchitis only since 5 years, which can be explained by the fact, that he has been smoking for many years. This patient did not have nasopharyngeal complaints. Furthermore he has 2 children. This patient nevertheless was included in the study because as stated in the introduction according to Afzelius' hypothesis every patient with dextrocardia must have some form of congenital ciliary malfunction.

As shown in figure 7 the mean clearance of the CB patients is not significantly different from the mean uncorrected clearance of the DC patients and neither from the mean of the "sputum corrected" clearance of the DC patients. The mean tracheobronchial clearance of the healthy non-smoking subjects is significantly faster than the other curves. The CB patients were older than the DC patients. The mean age was 58 and 30 years respectively. As reported by Puchelle clearance rate declines with age.[21] Furthermore it should be taken into consideration that all CB patients were current smokers. Four DC patients were non-smokers. Long-term smoking impairs tracheobronchial clearance.[22] Comparing the results of the measurement of tracheobronchial clearance of the DC patients with those of the CB patients these 2 factors, age and smoking habit, should be taken into account. In patients no.1 and 3 tracheobronchial clearance was severely impaired or absent, being in accordance with views and data in literature. However in the remaining 4 patients there exists obvious tracheobronchial clearance, even after correcting for cough. Tracheobronchial clearance was measured for 6 hours. It is practically impossible for these patients not to cough for such a long period. The main problem was therefore to correct for so-called cough clearance. Sometimes part of the sputum is swallowed. Consequently cough clearance will be underestimated. It is possible that this may have occurred sometimes. However, correcting for expectorated sputum in the manner described above leads in itself to an underestimation of the effect of tracheobronchial clearance other than by coughing. Because this correction implies that activity present in sputum would not have been cleared at all otherwise. Which mechanism could explain the observed clearance in four of the 6 DC patients? According to the literature two possible mechanisms responsible for tracheobronchial clearance other than by cough and/or mucociliary clearance are two-phase gas-liquid interaction and stop and go transport in peripheral airways. In vitro studies suggest, that two-phase gas-liquid interaction may be of importance in patients with abundant bronchial secretion.[23,24] It remains to be proven though whether this mechanism is effective in vivo. Another interesting phenomenon has been described as stop and go particle transport in the peripheral airways.[25] This implies unidirectional transport of particles in a fluid film solely under the influence of compression and expansion of this film. The effectiveness of this mechanism in vivo needs confirmation also.

Finally the results of this study seem to stress the necessity of both EM examination and dynamic studies of coordination and beat frequency of bronchial cilia in these patients.

In conclusion the results of this study are in agreement with those reported by Pavia et al.[20] They indicate, that in some patients with dextrocardia, including patients with Kartagener's syndrome, there exists a decreased but effective tracheobronchial clearance which can not be attributed to coughing alone.

Acknowledgements:

We thank F. Kuyper, pediatrician, Dept. of Pediatrics of the St. Radboudhospital, for referring patient no. 5, and H. Hassing, chest physician in the St. Maartens Gasthuis in Venlo, for referring patient no. 6.

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Chapter VIII

Sauna does not enhance tracheobronchial clearance in chronic bronchitics

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Introduction

The rehabilitation program for patients with pulmonary diseases in the University Lung Centre Nijmegen included the regular use of sauna. Many patients with chronic bronchitis and abundant sputum production indicated that during or after sauna expectoration seemed to be improved. It appeared therefore that sauna might provide an alternative for chest physical therapy with regard to clearance of excessive bronchial secretions. Therefore a study was performed to evaluate the effect of sauna on tracheobronchial clearance in chronic bronchitics.

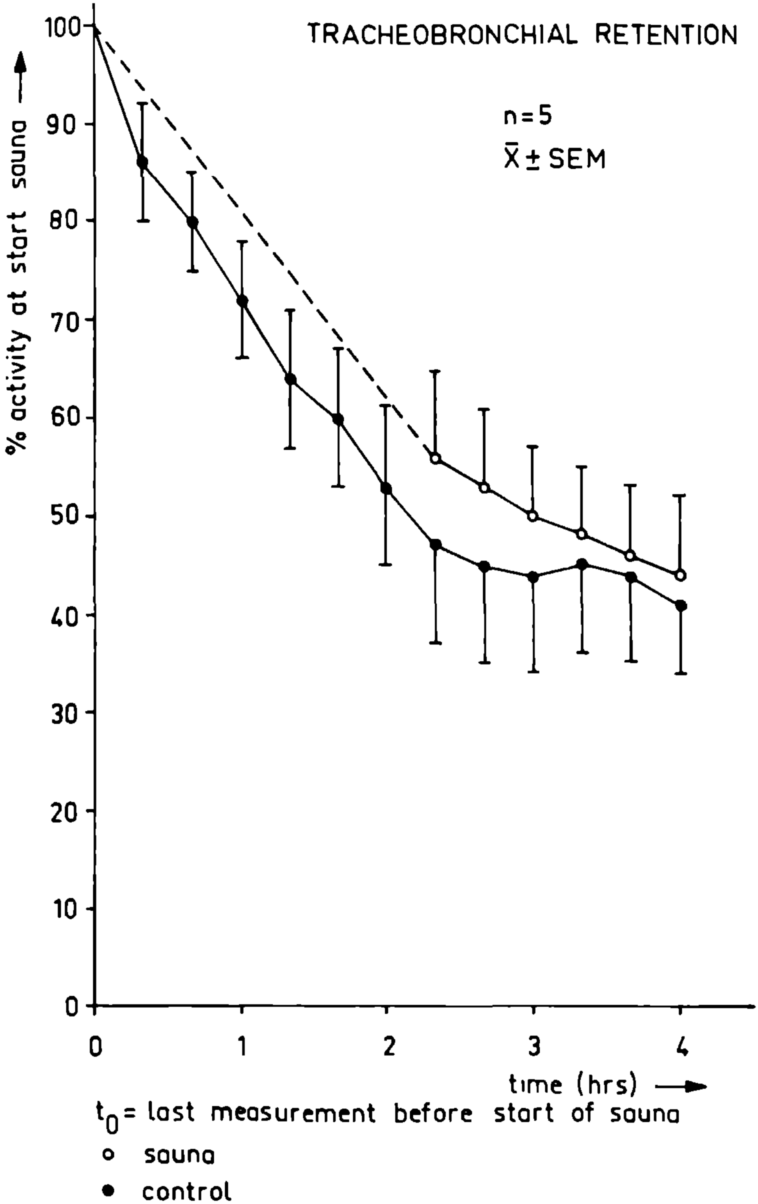
Patients and methods

Five male patients with chronic bronchitis according to the MRC criteria[1] took part in the study. Their mean age was 52 yrs (range 41-67 yrs). The mean forced expiratory volume in one second (FEV_1) was 69 (SD ± 9)% predicted. The mean vital capacity was 92 (SD ± 14)% predicted. Tracheobronchial clearance was measured by means of a radio-aerosol technique as described in more detail in an earlier publication[2]. A 5 μm ^{99m}Tc-labelled polystyrene particle aerosol was inhaled under standardized conditions. Subsequently intrathoracic radioactivity was measured at regular intervals by means of two scintillation detectors. As described by Pavia et al[3] the sum of the radioactivity count rates of the two detectors was corrected for background activity, physical decay of the radionuclide and 24 h retention. The tracheobronchial retention curve was obtained by plotting the percentages retention against time. The mean tracheobronchial retention curve was obtained using the interpolated percentages of the individual retention curves at twenty minute intervals. The last measurement prior to sauna or in the control measurement an equivalent span of time after inhalation of the radio-aerosol was defined as t_0 i.e. approximately 30 minutes after inhalation. Tracheobronchial retention is expressed as percentage of activity measured at t_0.

In a randomized cross-over fashion tracheobronchial clearance was measured on two separate days. During one of these measurements the patients attended a standardized sauna program. Immediately after t_0 patients went into the sauna for one and a half hours. No measurements were performed during this period. After completion of the sauna program the measurement of tracheobronchial clearance was resumed for approximately 2 hours. The other measurement of tracheobronchial clearance served as a control. The sauna program included two identical cycles. Each cycle began with a hot shower followed by a ten minute stay in the hot cabin (air temperature ± 90°C, relative humidity ± 15%). Then the subjects had a cold shower and underwent 3 immersions in a cold water basin. This was followed by a resting period (± 15 min.). The Wilcoxon test for paired data was used to evaluate the significance of any differences observed.

Results

The mean tracheobronchial retention curves of the two measurements (sauna and control) are presented in the figure. No significant differences were observed between the two measurements.



Tracheobronchial retention during and after sauna and during a control measurement in 5 patients with chronic bronchitis.

Conclusion

It is concluded that sauna does not enhance tracheobronchial clearance in patients with chronic bronchitis. Therefore sauna can be no substitute for chest physical therapy.

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Final discussion

On the basis of the results of the study described in chapter II it is concluded that tracheobronchial clearance in healthy non-smoking subjects has considerable inter-subject variability. Is there an explanation for the rather large variability between subjects? One explanation could be the difference in deposition pattern between individuals as a consequence of differences in anatomy and mode of inhalation of the radio-aerosol. Another variable is ciliary beat frequency. Duchateau et al[1] reported a significant correlation between nasal ciliary beat frequency and nasal mucus transport rate in healthy volunteers. It seems plausible that the same correlation exists for mucociliary transport rate in the lower airways. Furthermore the rheological characteristics of bronchial secretion probably play a role in individual clearance rate also. However, little is known about this relationship, not surprisingly, because the assessment of rheological properties of respiratory mucus in healthy subjects is difficult.

In the chapters III-VI studies are described on the efficacy of several physiotherapeutic interventions. One could argue that the number of patients included in these studies is rather small. On the basis of the data listed in table 3 of chapter II it can be concluded that a number of 8 subjects is sufficient to detect a 10% difference in tracheobronchial clearance at 2 hours after the start of the measurement and/or intervention. These numbers are based on the results of the measurement of tracheobronchial clearance in healthy individuals though. It is well known from the literature that variability of tracheobronchial clearance is larger in patients with chronic bronchitis. So the minimum change in tracheobronchial clearance due to a particular intervention must be somewhat larger than 10% in order to be detected in a cross-over trial including 8 subjects. As it was decided that for this type of treatment a direct effect amounting to at least 15-20% increase or decrease of tracheobronchial clearance must be considered as being clinically relevant, a number of 8 subjects seems to be sufficient.

The results of the studies described in the chapters III-V show that postural drainage is a very important component of chest physical therapy. However, patients experience postural drainage as rather unpleasant. McDonnell et al[2] reported that during chest physiotherapy including postural drainage in patients with cystic fibrosis, significant desaturations occurred. Desaturation could not be prevented by supplemental oxygen. The authors concluded that a possible explanation could be an increase in ventilation-perfusion mismatch due to blocking of airways by mucus plugs. It is therefore understandable that clinicians and physiotherapists are looking for alternatives to improve bronchial drainage effectively without the need of postural drainage. However, the results of the studies described in chapters III-V imply, that bronchial drainage procedures should include, if possible, postural drainage. Furthermore the combination of postural drainage and the forced expiration technique should be preferred for treatment of patients requiring regular (daily) chest physical therapy. It seems important to realize also that the duration of any bronchial drainage procedure should be limited in view of good so-called patient compliance.

In chapter VI a study on the efficacy of an inhaled mucolytic in combination with the forced expiration technique is described. As mentioned in the discussion of this chapter the results suggest that any difference in effectiveness of any of the three aerosol solutions has been annihilated by the subsequent forced expiration technique session which was combined with postural drainage. It seems therefore interesting to repeat a similar study without the physical therapy component. Such a study should preferably include a control measurement i.e. without any treatment. In our study a design including aerosol treatment combined with a bronchial drainage procedure was chosen because this is a frequently applied combination in clinical practice.

In recent years an increasing number of studies has been published with regard to primary ciliary dyskinesia. It has become clear that this syndrome consists of several types of anatomical and functional abnormalities of the mucociliary transport system. In the light of Afzelius' hypothesis patients with dextrocardia by definition are suffering from primary ciliary dyskinesia. Some of these patients indeed show the classical Kartagener's syndrome. In other patients, this is less evident. Investigations of these patients, as recommended in the discussion of chapter VIII, are possible only in well equipped laboratories and are not part of daily routine. Sometimes the implications of such investigations seem to be trivial. Therapeutic strategy usually is not influenced by the results thereof. For individual patients it can be of importance to know the chance of having descendants.

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Summary

In chapter I a brief review of the literature on tracheobronchial clearance is presented. Physiological aspects like structure and function of airway epithelium, mucociliary transport and cough are reviewed (section I.1). Aspects of tracheobronchial clearance in several disease states are discussed in section I.2. Techniques for the measurement of tracheobronchial clearance, which have been described in the past, and the technique, which was used in our laboratory, are discussed in section I.3 and section I.4. Briefly, this technique implied the inhalation of a radio-aerosol, consisting of 5 μm ^{99m}Tc labelled posystyrene particles. After inhalation intrathoracic radioactivity was measured at regular intervals by means of two scintillation detectors. The decrease in intrathoracic radioactivity, corrected for physical decay, background activity and alveolar deposition, was assumed to reflect tracheobronchial clearance. In section I.4 an outline of the study is presented also.

The first study, which is described in chapter II, deals with the variability of tracheobronchial clearance in healthy non-smoking subjects. Clearance was measured twice in ten volunteers to evaluate both inter- and intrasubject variability. For the measurement of tracheobronchial clearance the radioaerosol technique described in section I.4 was used.

Several parameters were used to quantitate the results of this measurement. Among those was the area under the retention curve up to 6 hours after inhalation (AUC-6). The intersubject coefficient of variation (COV) using this parameter was 31%. The intrasubject COV of the AUC-6 was 11%. These results compare favourably with those reported by others using different techniques. It is concluded that the intrasubject variability of tracheobronchial clearance as measured by this technique is small. Furthermore studies, in which tracheobronchial clearance is used as a parameter, should preferably be of the cross-over type.

In the first study (chapter III) on the effect of physiotherapeutic interventions on tracheobronchial clearance two frequently used regimens were compared with each other: conventional chest physiotherapy and the forced expiration technique. Conventional physiotherapy included postural drainage, percussion and directed coughing.

The forced expiration technique included breathing exercises, huffing, if necessary coughing and postural drainage. Eight patients (six with cystic fibrosis and two with agammaglobulinaemia) took part in the study. Both techniques appeared to be equally effective with regard to tracheobronchial clearance, regional lung clearance, sputum production and lung function. Because the forced expiration technique after proper instruction and training can be performed without an assistant, this technique seems preferable in daily routine.

In chapter IV two studies are described, both on positive expiratory pressure mask physiotherapy. In a randomized cross-over trial (section IV.1.), including a control measurement, the effect of positive expiratory pressure mask physiotherapy and of the forced expiration technique on tracheobronchial clearance was evaluated in eight chronic bronchitics with abundant sputum production (mean 32 g/day). Positive expiratory pressure mask physiotherapy included positive expiratory pressure mask breathing interspersed with breathing exercises, huffing and if necessary coughing, but no postural drainage. The forced expiration technique included breathing exercises, huffing and if necessary coughing combined with postural drainage.

Clearance was measured by means of the radio-aerosol technique described in section I.4. At 40 min. after the start of therapy the mean clearance, expressed as percentage of the amount of radioactivity present at the start of therapy, was 32% after positive expiratory pressure mask physiotherapy, 53% after the forced expiration technique session, and 15% in the control run. These differences were statistically significant ($P < 0.02$). Sputum production during positive expiratory pressure mask physiotherapy and the forced expiration technique session was larger than during the equivalent period of time in the control run. It is concluded that both positive expiratory pressure mask physiotherapy and the forced expiration technique enhance tracheobronchial clearance. Furthermore it appeared that the forced expiration technique, combined with postural drainage is more effective than positive expiratory pressure mask physiotherapy.

In the following section (IV.2.) the effect of positive expiratory pressure mask physiotherapy on regional lung clearance is evaluated. Regional lung clearance was estimated by means of gamma camera imaging. The results after positive expiratory pressure mask physiotherapy were not significantly different from control. The mean clearance in all three lung zones (peripheral, intermediate and inner) was largest after the forced expiration technique session including postural drainage. Statistical significance ($p \leqslant 0.02$) was reached only for clearance after the forced expiration technique in the inner region. It is concluded that positive expiratory pressure mask physiotherapy has no demonstrable effect on regional lung clearance.

A study in which the effect of oral high frequency oscillation on tracheobronchial clearance was evaluated is described in chapter V. In a randomized cross-over trial including a control measurement oral high frequency was compared with the forced expiration technique. Eight patients with chronic bronchitis were investigated (mean sputum production 33 ± 9 g/day). Oral high frequency oscillation was applied at the respiratory system resonant frequency of each patient (range 9-25 Hz) and combined with huffing. The forced expiration technique included breathing exercises, huffing, if necessary coughing and postural drainage. Tracheobronchial clearance was measured by means of the radio-aerosol technique described in section I.4. At 60 minutes after start of the treatment mean tracheobronchial retention, expressed as percentage of the activity at the start of the treatment, was 70 ± 26% after oral high frequency oscillation, 54 ± 26% after the forced expiration technique session and 76 ± 18% in the control run, which included huffing only. Oral high frequency appeared to be not significantly different from control. The forced expiration technique was significantly different ($p<0.02$) from both OHFO and control. It is concluded that oral high frequency oscillation has no effect on tracheobronchial clearance in chronic bronchitics.

The effect of an inhaled mucolytic in combination with the forced expiration technique on tracheobronchial clearance was investigated in the study described in chapter VI. Eight patients with chronic bronchitis and abundant sputum production inhaled on three separate days in a double blind randomized cross-over fashion one of the following nebulized solutions: (A) mercaptoethane sulphonate (Mistabron^R), (B) hypertonic saline and (C) isotonic saline. Inhalation of each solution was followed by a forced expiration technique session. Clearance was measured using the radio-aerosol technique described in section I.4. No significant differences between the three treatments were found. It is concluded that there exists no significant difference in effectiveness of inhalation of Mistabron^R, hypertonic saline or isotonic saline when combined with a forced expiration session including postural drainage.

Tracheobronchial clearance in patients with dextrocardia is reported in chapter VII. In six patients with dextrocardia tracheobronchial clearance was measured by means of the radio-aerosol technique described in section I.4. The tracheobronchial retention curves were corrected for expectorated sputum in order to rule out as much as possible the effect of cough-clearance. In two patients clearance after sputum correction was practically absent i.e. six hours after inhalation there was 82 and 83% retention. In the remaining four patients retention percentages of 56, 55, 46 and 42% were assessed. The mean tracheobronchial retention of all dextrocardia patients was significantly larger than the mean retention in ten healthy non-smoking subjects, but not significantly different from that of six chronic bronchitics. It is concluded that in some patients with dextrocardia, patients with the syndrome of Kartagener included, a decreased but effective tracheobronchial clearance exists, which cannot be attributed to cough alone.

Finally in chapter VIII a study is described in which the effect of sauna on tracheobronchial clearance in chronic bronchitics has been investigated. Five patients with chronic bronchitis took part. Tracheobronchial clearance was measured using the radio-aerosol technique described in section I.4. In a randomized cross-over fashion the effect of sauna was compared with a control measurement. Sauna appeared not to enhance tracheobronchial clearance.

Samenvatting

In hoofdstuk I wordt een overzicht gegeven van de literatuur betreffende tracheobronchiale klaring. Aspekten zoals struktuur en funktie van het luchtwegepitheel, het mucociliair transport en hoesten worden belicht (sectie I.1). De tracheobronchiale klaring in relatie tot diverse longziekten wordt besproken in sectie I.2. In sectie I.3 worden diverse technieken beschreven, welke in het verleden toegepast zijn om de tracheobronchiale klaring te meten. De techniek, welke in ons laboratorium is gebruikt wordt beschreven in sectie I.4. Kort samengevat is het principe van deze meting als volgt. Na inhaleren van een radio-aerosol, bestaande uit radioactief gelabelde polystyreen partikels, wordt regelmatig de hoeveelheid radioactiviteit in de longen gemeten met behulp van twee scintillatie detectoren. De afname van de activiteit, na correctie voor verval, achtergrond activiteit en alveolaire depositie, is een maat voor de tracheobronchiale klaring. In deze sectie wordt ook de opzet van het onderzoek als geheel uiteen gezet.

Het eerste onderzoek, beschreven in hoofdstuk II, betrof het vaststellen van de variabiliteit van de tracheobronchiale klaring bij gezonde, niet rokende proefpersonen. Om zowel de inter- als intra-individuele variabiliteit te kunnen evalueren werd de klaring tweemaal gemeten bij tien vrijwilligers. Voor het meten van de tracheobronchiale klaring werd gebruik gemaakt van de hierboven aangeduide radio-aerosol techniek. Verschillende parameters werden gebruikt voor het kwantificeren van de meetresultaten. Onder andere werd gekeken naar het oppervlak onder de retentiecurve vanaf het moment van inhalatie tot 6 uur daarna (AUC-6). De interindividuele variatiecoëfficiënt (COV) bij gebruik van deze parameter was 31%. De intra-individuele COV van de AUC-6 was 11%. Onze resultaten zijn beter dan die gerapporteerd door andere onderzoeksgroepen, die gebruik gemaakt hebben van andere meettechnieken. Geconcludeerd wordt dat de intra-individuele variabiliteit van de tracheobronchiale klaring, zoals gemeten middels deze techniek, gering is.

In de eerste studie naar het effect van fysiotherapeutische interventies op de tracheobronchiale klaring werden twee vaak toegepaste behandelingstechnieken met elkaar vergeleken: conventionele fysiotherapie en geforceerde expiratie techniek (hoofdstuk

III). Conventionele fysiotherapie omvatte houdingsdrainage, tapotage en hoesten. De geforceerde expiratie techniek omvatte ademhalingsoefeningen, huffen, houdingsdrainage en indien nodig, hoesten. Onder huffen wordt verstaan het geforceerde uitademen met open stemspleet volgend op een normale inademing. Acht patiënten, waarvan zes met mucoviscoidosis en twee met agammaglobulinemie, namen deel aan deze studie. Deze twee behandelingstechnieken bleken even effektief wat betreft tracheobronchiale klaring, regionale klaring, sputum produktie en longfunktie. Omdat de geforceerde expiratietechniek na instruktie en oefening zonder hulp kan worden toegepast lijkt deze techniek voor de dagelijkse praktijk de voorkeur te verdienen.

In hoofdstuk IV worden twee onderzoeken beschreven naar het effekt van behandeling met het zogenaamde positieve expiratoire druk (PEP) masker. In een gerandomiseerde cross-over studie (IV.1) werd het effekt op de tracheobronchiale klaring van behandeling met het PEP-masker vergeleken met dat van de geforceerde expiratie techniek. Dit onderzoek omvatte tevens een controlemeting. Acht patiënten met een chronische bronchitis en overvloedige sputum produktie (gemiddeld 32 gram per dag) namen eraan deel. De behandeling met het PEP masker omvatte het gebruik van het PEP masker afgewisseld met ademhalingsoefeningen, huffen en indien nodig hoesten. Daarbij werd geen houdingsdrainage toegepast. De geforceerde expiratie techniek was dezelfde als die beschreven in hoofdstuk III. Voor het meten van de tracheobronchiale klaring werd gebruik gemaakt van dezelfde radio-aerosol techniek als beschreven in sectie I.4. Veertig minuten na het begin van de behandeling was de gemiddelde klaring, uitgedrukt als percentage van de hoeveelheid aktiviteit aanwezig bij het begin van de behandeling, 32% na de behandeling met het PEP masker, 53% na de geforceerde expiratietechniek en 15% in de controle-meting. De verschillen waren statistisch significant ($p < 0.02$). De sputum produktie tijdens beide behandelingsvormen was significant groter dan tijdens de controlemeting ($p < 0.02$). Geconcludeerd wordt dat beide behandelingsvormen effekt hebben. De geforceerde expiratie techniek blijkt echter effektiever dan de behandeling met het PEP-masker. In de volgende sectie (IV.2) wordt het effekt van de behandeling met het PEP masker op de regionale longklaring beschreven. De regionale longklaring werd gemeten met behulp van gamma camera opnames. De resultaten van de behandeling met het PEP masker waren niet significant verschillend van die tijdens de controle meting. De gemiddelde klaring in alle drie longzônes (perifeer, intermediair en centraal) was het grootst na de geforceerde expiratie techniek sessie, welke ook houdingsdrainage omvatte. Alleen de klaring na de geforceerde expiratie techniek in de centrale zône was statistisch significant ($p \leq 0.02$) verschillend van de behandeling met het PEP masker en de controle meting. Geconcludeerd wordt dat de behandeling met PEP geen aantoonbaar effekt heeft op de regionale klaring.

In hoofdstuk V wordt het onderzoek beschreven, waarin het effekt van orale hoogfrekwente oscillatie (OHFO) op de tracheobronchiale klaring is geëvalueerd. OHFO werd vergeleken met de geforceerde expiratie techniek en met een controle meting. Acht patiënten met chronische bronchitis namen deel aan de studie. De frekwentie, waarop OHFO werd toegepast, kwam overeen met de individuele resonantiefrekwentie van het luchtwegsysteem van de patiënt. OHFO werd gecombineerd met huffen. De geforceerde expiratie techniek was hetzelfde als in bovenbeschreven onderzoeken (hoofdstuk III en IV). Ook voor de meting van de tracheobronchiale klaring werd gebruik gemaakt van dezelfde radio-aerosol techniek als beschreven in sectie I.4. Zestig minuten na het begin van de behandeling was de gemiddelde tracheobronchiale retentie 70 ± 26% na OHFO, 54 ± 26% na de geforceerde expiratie techniek en 76 ± 18% in de controle meting, welke alleen huffen omvatte. Het effekt van OHFO was niet significant verschillend van dat tijdens de controle. Het effekt van de geforceerde expiratie techniek was significant verschillend ($p < 0.02$) van dat van OHFO en dat van de controlemeting. Geconcludeerd wordt dat OHFO geen effekt heeft op de tracheobronchiale klaring bij patiënten met chronische bronchitis.

In hoofdstuk VI wordt het onderzoek beschreven, waarin het effekt op de tracheobronchiale klaring van een geïnhaleerd mucolyticum gecombineerd met de geforceerde expiratie techniek, werd geëvalueerd. Acht patiënten met chronische bronchitis en overmatige sputum produktie inhaleerden op drie verschillende dagen, waarbij de volgorde at random en dubbelblind werd vastgesteld, een van de volgende drie vernevelde oplossingen: een oplossing bevattende mercapto-ethaan sulfonzuur (Mistabron[R]), een hypertone en een isotone zoutoplossing. Het inhaleren van iedere oplossing werd gevolgd door een sessie bestaande uit de geforceerde expiratie techniek met houdingsdrainage.De tracheobronchiale klaring werd gemeten met behulp van de eerder beschreven radio-aerosol techniek (sectie I.4). Er werden geen significante verschillen in effekt van de drie behandelingen gevonden, zodat geconcludeerd kan worden dat Mistabron[R] geen toegevoegde waarde heeft.

In hoofdstuk VII worden de resultaten van de meting van de tracheobronchiale klaring bij zes patiënten met dextrocardie beschreven. De tracheobronchiale klaring werd gecorrigeerd voor het effekt van hoesten door de resultaten van de meting van de radioaktiviteit in de longen te corrigeren voor de radioaktiviteit gemeten in opgehoest sputum. Bij twee patiënten bleek de klaring na toepassing van deze correctie nagenoeg afwezig. Er was een retentie van 82 en 83% na 6 uur. Bij de overige vier patiënten bedroeg het retentiepercentage 56, 55, 46 en 42%. De gemiddelde tracheobronchiale retentie van de patiënten met dextrocardie was significant groter dan die van tien gezonde niet rokers. De gemiddelde tracheobronchiale retentie van de zes dextrocardie patiënten was niet significant verschillend van die bij zes patiënten met chronische bronchitis. Kennelijk is er bij sommige patiënten met dextrocardie, inclusief patiënten met het syndroom van Kartagener, een effektieve tracheobronchiale klaring die niet kan worden toegeschreven aan het effekt van hoesten.

Tenslotte wordt in hoofdstuk VIII een onderzoek beschreven waarin het effekt van sauna op de tracheobronchiale klaring bij vijf patiënten met chronische bronchitis werd bestudeerd. Het effekt van sauna werd vergeleken met een controle meting. Er was geen effekt van sauna op de tracheobronchiale klaring aantoonbaar.

Woorden van dank

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Demetri Pavia, MSc, PhD, FInst P, who was at the time principal scientific officer of the department of Thoracic Medicine (head: dr. S.W. Clarke, MD, FRCP) of the Royal Free Hospital in London, appeared to be willing to share with me wholeheartedly his vast experience and knowledge in the field of mucociliary transport and aerosols.

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Curriculum vitae

De auteur van dit proefschrift werd op 22 september 1950 geboren te Arnhem. In 1968 behaalde hij het diploma Gymnasium-ß aan het Katholiek Gelders Lyceum te Arnhem. Vervolgens studeerde hij geneeskunde aan de Katholieke Universiteit te Nijmegen. In februari 1978 behaalde hij het artsexamen.

In maart van dat jaar begon de opleiding tot internist in het St. Elisabeth Ziekenhuis te Amersfoort (opleider: Dr. D. Bonte). Na 1 maart 1980 werd deze opleiding voortgezet in de Kliniek voor Inwendige Ziekten van het Academisch Ziekenhuis te Nijmegen (opleider destijds: Prof.Dr. C.L.H. Majoor, nadien: Prof.Dr. A. van 't Laar). Op 1 maart 1983 volgde inschrijving als internist in het specialistenregister. Op 1 januari 1983 werd gestart met de opleiding tot longarts (opleider destijds: Prof. C.M. Jongerius, nadien Prof.Dr. C.L.A. van Herwaarden). In februari 1985 werd de opleiding onderbroken voor de periode van 2 jaar en 8 maanden. De eerste 2 maanden hiervan werden doorgebracht op het Research Laboratorium (hoofd: Dr. D. Pavia, MSc, PhD, IFnst P) van de afdeling 'Thoracic Medicine' (hoofd: Dr. S.W. Clarke, MD, FRCP) van het Royal Free Hospital te Londen.

Gedurende de resterende periode van 2 jaar en 6 maanden lag de nadruk op het verrichten van onderzoek, hetgeen uiteindelijk geresulteerd heeft in dit proefschrift. Op 1 oktober 1988 werd de opleiding tot longarts officieel hervat. Op 1 september 1989 volgde de inschrijving als longarts in het specialistenregister. Tot 1 januari 1990 was hij werkzaam als longarts op het Universitair Longcentrum Nijmegen, bestaande uit de afdeling Longziekten van het Sint Radboudziekenhuis te Nijmegen en het Medisch Centrum Dekkerswald te Groesbeek. Sindsdien is hij als longarts werkzaam in het Andreas Ziekenhuis te Amsterdam in associatie met T.K.G. Deves, longarts.

Stellingen bij het proefschrift
'The effect of several physiotherapeutic interventions on tracheobronchial clearance'
door M. van Hengstum

I

Het optimale bronchiaaltoilet bestaat uit de geforceerde expiratietechniek in combinatie met houdingsdrainage.

(dit proefschrift)

II

In tegenspraak met de theoretische overwegingen hieromtrent heeft het zogenaamde PEP-masker geen effect op de klaring in de perifere luchtwegen.

(dit proefschrift)

III

Het inhaleren van een mucolyticum blijkt de tracheobronchiale klaring niet meer te bevorderen dan inhalatie van een hypertone of isotone zoutoplossing.

(dit proefschrift)

IV

Orale hoogfrekwente oscillatie blijkt geen aanwinst in de behandeling van patiënten met overmatige sputumproduktie.

(dit proefschrift)

V

Sauna mag dan vaak het algemeen welbevinden bevorderen, echter niet de tracheobronchiale klaring.

(dit proefschrift)

VI

Bij patiënten met een kleincellig bronchuscarcinoom, die een respons vertonen op chemotherapie, is het voortzetten van de behandeling na zes kuren niet zinvol.

Spiro SG, Souhami SL. Thorax 1990;45:1.

VII

Bij stervensbegeleiding dient ervoor gewaakt te worden de behandeling van de terminale patiënt mede te laten bepalen door onrust, onzekerheid of medelijden onder aanwezige naasten.

VIII

Het verloop van een bronchoscopie kan in sommige gevallen in gunstige zin worden beïnvloed door de patiënt mee te laten kijken bij de inspectie van diens bronchiaalboom.

(eigen waarneming)

IX

Twee procent lidocaine spray is voor het verwijderen van exemplaren van de Periplaneta Americana uit de gehoorgang meer geschikt dan het gebruik van minerale olie.

O'Toole K et al. NEJM 1985;312(18):1197.

X

De methode gebruikt voor het corrigeren van gietfouten zoals beschreven door Cellini (1500-1574), levert een beter resultaat op dan moderne lastechnieken.

(eigen waarneming)

XI

De promovendus dient zelf de stellingen behorend bij zijn proefschrift te bedenken.